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CLINICAL USE OF EXTRACT OF THE ADRENAL CORTEX

REPORT ON THIRTY-FOUR CASES OF ADDISON'S DISEASE STUDIED BETWEEN 1930 AND 1937, WITH A REVIEW OF THE LITERATURE

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The recognition of the functions of the various endocrine glands and of the importance of the hormones which they produce is one of the recent developments in medicine. The adrenal glands, for example, were described by Eustachius in 1563, but nearly three hundred years elapsed before there was any real insight into their physiologic activity. In 1855 Addison pointed out the constitutional effects of disease of these glands and established the clinical syndrome which bears his name. The experiments of Oliver and Schäfer in 1895 paved the way for the isolation and chemical identification of epinephrine by Abel and Takamine a few years later.

The last-mentioned discovery focused attention on the medullary portion of the adrenal gland, and the majority of subsequent investigations have dealt with the functional activity of the medulla. Other experiments, however, have been concerned with the effects of partial or complete extirpation of these glands. These experiments, the results of which have recently been summarized by Britton, established beyond question the uniformly fatal effect of total adrenalectomy in practically all laboratory animals. They have further emphasized the preponderant rôle of the cortical portion of the gland in the maintenance of life after partial adrenalectomy. Epinephrine is ineffective in maintaining life in such animals, and efforts to isolate the active principle or principles from the adrenal cortex were unsuccessful for a long time. Banting and Gairns, Rogoff and Stewart, Hartman and his associates and many others made pioneer investigations in this field, but the first evidence that the life of a totally adrenalectomized cat can be prolonged indefinitely by the administration of an extract of the adrenal cortex was presented in 1930 by Swingle and Pfiffner. Hartman and Brownell, working independently of these investigators, reported similar results

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a few weeks later. These workers used lipoid solvents for the extraction of the active principle.

The activity of extracts prepared in this manner has been confirmed by numerous investigators, and it is now recognized that totally adrenalectomized animals can be kept alive and in a state of normal health for an indefinite period by the continuous administration of adrenal extracts. Numerous recent investigators, among whom may be mentioned Swingle and Pfiffner; Grollman and Firor; Zwemer; Zwemer, Agate and Schroeder, and Pfiffner, Vars and Taylor, have reported the preparation of purified extracts of great potency, while Kendall and his associates have described the crystallization of an active principle. It is probable, therefore, that in the near future the chemical structure of the cortical hormone will be determined and that the purified product will become available for general use in therapy. Consequently, it is fitting to review the experience with the use of the present cruder extracts, so that it may be determined in what fields of medicine the purified product is likely to be of greatest usefulness.

Reference should be made to various comprehensive reviews, such as those of Britton, Swingle and Pfiffner, Harrop and Hartman, for a discussion of the effects of total adrenalectomy in experimental animals and of the response of such animals to the administration of a cortical extract. No certain criterion of the degree of adrenal insufficiency has been described. The ability of an extract to maintain a totally adrenalectomized animal in a state of health indefinitely is still the final test of its potency. Swingle and Pfiffner in 1932 made the following statement, which is still valid:

> The real functional significance of the cortical hormone is unknown. All of the changes reported as occurring in the organism following bilateral adrenalectomy, we regard as secondary to some at present unknown, underlying derangement of the animal. . . . The literature is filled with theories and hypotheses of adrenal function. . . . No one has yet succeeded in presenting definite, clear-cut, unequivocal evidence of cortical function. . . . The function of the adrenal cortex is a subtle and intriguing one, but the solution is not yet at hand.

Adrenal cortex extract has been used most frequently and with most dramatic results in the treatment of Addison's disease. Certain features of the clinical course of this disease must be kept in mind in considering the effects of treatment. Addison's disease, as shown in the tabulation of Guttman, is almost always due either to bilateral tuberculosis or to bilateral contraction (cortical atrophy) of the adrenal glands. The proportion of cases in which tuberculosis is present varies, depending on the series cited, from 70 to 85 per cent of the total number. The course of the disease usually is of progressively increasing severity. In occasional cases the condition may be stationary for a long time, as in the instance (reported by Snell) in which the patient had been under observation for seventeen years. Sooner or later, how-

ever, there is acute exacerbation, with crisis and death. The disease is usually rapidly fatal. In 88 cases in which no treatment was given, selected from the records of the Mayo Clinic, the average length of life was one and eighty-two hundredths years, and in half of the cases the patient died within one and twenty-seven hundredths years. The duration of life in 266 cases in which there was no treatment is given in the accompanying table. This table includes data on the 88 cases from the Mayo Clinic and 178 cases the reports of which were compiled by Guttman. It shows that only 71.4 per cent of the total number of patients lived more than six months, 51.3 per cent more than one year and 10.5 per cent four years after the onset of definite symptoms.

Results of Observations in Cases of Addison's Disease Showing Comparative Duration of Illness in 34 Cases Studied from 1930 to 1937 in Which Treatment with Adrenal Extract Was Given and in 266 Cases in Which No Treatment Was Given *

Period of Survival of Patients	Percentage of Patients Who Survived	
	Patients Receiving No Treatment	Patients Receiving Treatment
6 months or more	71.4	88.2
1 year or more	51.3	67.6
1½ years or more	36.5	55.8
2 years or more	31.2	49.9
2½ years or more	20.7	44.0
3 years or more	18.4	38.1
3½ years or more	11.3	35.2
4 years or more	10.5	29.3
4½ years or more	....	23.5
5 years or more	7.5	....
5½ years or more	6.4	....
6 years or more	5.6	18.8
8 years or more	4.5	....
10 years or more	1.5	14.1

* Prof. W. W. Swingle, of Princeton University, and Dr. Oliver Kamm, of Parke, Davis & Company, furnished supplies of extract which made the initial treatment of these patients possible. The work of Swingle and Pfiffner was aided in part by a grant from the Josiah Macy Jr. Foundation.

The clinical course in the usual case of Addison's disease, as pointed out by Greene, Rowntree, Swingle and Pfiffner, may be divided into three periods:

1. The period of initial destruction of the adrenal glands or latent adrenal insufficiency. Both the clinical and the experimental observations indicate that the adrenal glands possess considerable functional reserve. Clinically recognizable signs of adrenal insufficiency, or Addison's disease, do not appear until this reserve is seriously impaired or destroyed.

2. The period of the recognized clinical syndrome or partial adrenal insufficiency. The characteristic clinical symptoms of Addison's disease, namely, asthenia, pigmentation, loss of weight and strength and arterial hypotension, are well known. Once they appear, the diagnosis is established. In cases in which the diagnosis is doubtful, the roentgeno-

graphic demonstration of calcification of the adrenal glands, as pointed out by Ball, Greene, Camp and Rowntree and by Camp, Ball and Greene, is evidence of tuberculosis of the adrenals and so is of value in confirming the diagnosis.

3. The terminal period of crisis or total adrenal insufficiency. Patients with Addison's disease ordinarily have little resistance, even to the ordinary stress and strain of every-day existence. Intercurrent infection; exposure to cold or high temperatures; undue fatigue, whether physical or mental; gastro-intestinal disturbance; too active purgation; the unwise administration of drugs, such as insulin or thyroid extract, and minor trauma or operation, such as dental extraction or tonsillectomy, frequently serve as predisposing factors to initiate an acute condition resembling shock or a period of crisis. This condition is characterized by severe gastro-intestinal disturbance, nausea, vomiting, dehydration, pain, nervous irritability, circulatory collapse, low blood pressure, cold extremities, reduction in the output of urine and lowered body temperature. In the secondary stage, the basal metabolic rate may be reduced, and the sugar content of the blood is frequently low. In the period of crisis, these changes are more marked. In addition, hemoconcentration is high; the blood volume is reduced, and the viscosity of the blood is increased. The hemoglobin concentration, the urea and nonprotein nitrogen contents of the blood and the protein, calcium, potassium and inorganic sulfate contents of the serum are increased. The alkali reserve, the chloride content and, as Loeb pointed out, the sodium content of the serum are reduced. The similarity between the condition of a patient in the crisis of Addison's disease and that of a laboratory animal after complete adrenalectomy and the resemblance of both these states to the condition of surgical shock have been pointed out many times (Greene, Rowntree, Swingle and Pfiffner; Harrop; Sullivan, MacLean and Zwemer, and Swingle, Pfiffner, Vars, Bott and Parkins).

TREATMENT OF ADDISON'S DISEASE

The successful treatment of Addison's disease is difficult and calls on the resourcefulness of the physician to the fullest extent. It should be directed along four main lines: (1) treatment of the underlying disease, (2) protection of the patient, (3) symptomatic therapy and (4) specific organotherapy.

Treatment of the Underlying Disease.—Since in the majority of cases Addison's disease is due to tuberculosis, the problem of treatment of this disease is primarily the problem of the treatment of tuberculosis. It is, indeed, fortunate that involvement of the adrenals is so infrequent in tuberculosis. The cause of cortical atrophy is generally thought

to be unknown, so that therapy is difficult. Warthin, on the other hand, insisted that in many cases Addison's disease is due to latent syphilis. If this is correct, specific therapy is possible. Frank syphilis, though of infrequent occurrence, is perhaps the third most common cause of adrenal insufficiency in Addison's disease.

Protection of the Patient.—The sensitivity of the patient with a mild or moderate degree of adrenal insufficiency to the ordinary stress and strain of daily life and the ease and suddenness with which crisis may be precipitated have been mentioned. To avoid such an accident, the patient should be protected in every way possible. The danger of intercurrent infection, physical and mental fatigue and exhaustion, gastrointestinal disturbance, exposure to low or high temperatures or unwise medication and the importance of protection against such mishaps or, when they are unavoidable, of early and active treatment cannot be stressed too strongly.

Symptomatic Therapy with Particular Reference to Anhydremia and Shock.—Anhydremia and shock dominate the clinical picture both in a patient in crisis and in an experimental animal after complete adrenalectomy. Whether this is due to a primary function of the adrenal cortex in the regulation of the metabolism of water and salts, as claimed by Zwemer; Loeb; Harrop, and Swingle, Pfiffner, Vars, Bott and Parkins, or whether the condition is secondary to some yet uncharacterized function of the gland is perhaps an academic question. The value of injections of physiologic solution of sodium chloride or of Ringer's solution in prolonging the life of adrenalectomized animals has been recognized since the work of Soddu. The value of infusions of saline solution or of 10 per cent dextrose in physiologic solution of sodium chloride in the treatment of patients in crisis, as pointed out by Rowntree, Greene, Swingle and Pfiffner, was recognized before active adrenal extracts were available for clinical use. This is illustrated in the case reported by Wakefield, as well as in the cases recently described by Loeb and Harrop. I have seen several patients with Addison's disease who did not do well, even though sufficient fluid and saline solution were given to prevent dehydration and depletion of salt, and who improved when adrenal extract was given in addition. A similar case has recently been reported by Kincov, Zillessen and Rowntree. On the other hand, many patients with Addison's disease report a craving for salty foodstuffs, such as sauerkraut, ham, pickles and tomatoes with salt. One such youth ate salt with as much relish as a child eats sugar. The provision of an adequate intake of fluids and salt is essential to the management of Addison's disease.

During the past two years, abundant evidence cited by Loeb, Atchley and Stahl; Loeb; Harrop; Kepler, and others has been produced to

show that both adrenalectomized animals and patients with Addison's disease do better with an ample intake of sodium. Conversely, a reduction in the intake of sodium may precipitate a crisis of adrenal insufficiency and so be of diagnostic value in a case in which the diagnosis is doubtful.

Allers, Nilson and Kendall; Wilder and his associates; Allott, and Zwemer and Truszkowski have emphasized the harmful effects of retention of potassium in adrenalectomized animals and in patients with Addison's disease. Not only does the clinical condition of the patient show a closer correlation with the degree of retention of potassium than with the loss of sodium but in dogs the administration of potassium will precipitate a crisis of acute adrenal insufficiency. The most beneficial effects of an increased intake of sodium are not obtained in patients unless the intake of potassium salts is limited.

Specific Organotherapy.—Organotherapy is as old as the clinical recognition of the disease. The earlier results have been reviewed by Kinnicutt, Johnston and Adams. The more recent Muirhead treatment has been reported severally by Rowntree, by Snell and Rowntree and by Rowntree and Snell. These authors reported partial success with the latter method, in that it afforded palliation of symptoms in some cases and prolonged benefit in a few. Similar results were reported by Rogoff with the use of an extract of the adrenal cortex which he called interrenalin and by Goldzieher.

The most dramatic results of specific organotherapy have been obtained with the parenteral or intravenous use of active extracts of the type introduced by Swingle and Pfiffner and by Hartman and his collaborators. The first clinical use of an extract of this type was made in June 1930, when Rowntree and I treated a patient with extract prepared by the method of Swingle and Pfiffner. In January 1931 we reported on a series of 20 patients treated with the preparation of Swingle and Pfiffner. To date, I have had personal experience with the treatment in 34 cases of Addison's disease and, through correspondence, in an additional 7 cases which have not been reported. Search of the literature revealed a total of approximately 200 additional cases of Addison's disease in which preparations of the adrenal cortex were used therapeutically.[1] The results in the entire series agree and confirm the conclusions based on personal experience.

These results indicate that many analogies may be drawn between diabetes mellitus and Addison's disease. As the discovery of insulin was the final step in establishing the rôle of insufficiency of the islands of Langerhans in the pathogenesis of diabetes, the discovery of the cortical hormone has furnished final proof of the rôle of adrenal insuffi-

1. The articles are listed in the bibliography.

ciency in the pathogenesis of Addison's disease. Diabetes mellitus varies in severity. Cases are recognized in which the cardinal symptoms of diabetes are not shown but the carbohydrate tolerance is reduced—that is, the so-called prediabetic state. Mild diabetes can be controlled by dietary measures alone, but patients with more severe disease do better if they are given insulin in addition. The dose of insulin required is, in part, a measure of the severity of the disease. Insulin, furthermore, is of the greatest value in the treatment of diabetic coma. The treatment of the patient with diabetes and the necessary dose of insulin vary with the stage and severity of the disease. In Addison's disease, likewise, the plan of treatment and the necessary dose of adrenal cortex extract vary with the severity of the disease in each patient. In Addison's disease there is no convenient yardstick, like the sugar content of the blood or urine in diabetes mellitus, with which to measure the degree of the adrenal deficiency, though the necessary dose of adrenal cortex extract is an approximate measure.

Treatment of Crisis: As the most evident results of the therapeutic use of insulin occur in the treatment of diabetic coma, the most dramatic effects of treatment with adrenal cortex extract have been observed in patients in the crisis of acute adrenal insufficiency. The striking clinical changes in patients who respond satisfactorily to treatment are: (1) disappearance of anorexia, nausea and vomiting, reappearance of appetite and development of the sense of hunger; (2) relief from fatigue and increase in strength and endurance; (3) disappearance of pain and improvement in sleep; (4) decrease in pigmentation; (5) gain in weight; (6) return of normal gastro-intestinal activity; (7) disappearance of nervous irritability and restlessness and change in the mental attitude to one characterized by hope and euphoria; (8) elevation of the body temperature to a normal level; (9) moderate increase in blood pressure when the patient is in crisis or shock and little change when the patient is in good condition; (10) increased resistance to infection or to the effect of surgical procedure, and (11) partial or complete rehabilitation of the patient, with ability to work.

The most constant and striking effect is the disappearance of anorexia, nausea and vomiting and of the distressing pain in the loins that is present in so many patients with adrenal insufficiency. Increase in strength and endurance appears early and is marked and out of proportion to the objective effects. The decrease in pigmentation may become apparent within three or four days, but there was no change in many patients in the series reported in this paper.

The immediate therapeutic response was satisfactory in the majority of the cases in this series. Variations in the results are inevitable, depending on the condition of the patient when he is first seen. In 2 cases the patient was in severe shock at the time of observation and died

before adequate supplies of the extract could be obtained. One patient (case 15) did not respond satisfactorily and died in the hospital, though she was apparently given adequate treatment. This experience at first appears to be in striking contrast to the results of the experiments of Swingle and Pfiffner, who found that adrenalectomized animals, prostrate and about to die of adrenal insufficiency, could be restored to normal health by treatment with adrenal cortex extract. Bilateral adrenalectomy produces acute adrenal insufficiency in an experimental animal with normal reserves of strength and previously unimpaired vitality. The conditions for recovery of the patient with Addison's disease differ from those for the recovery of the adrenalectomized animals, for the patient suffers from a chronic ailment characterized by marked exhaustion and greatly reduced vitality. The recuperative power may be greatly reduced under these conditions, and it is not surprising that treatment may occasionally be without avail. Swingle and Pfiffner have also noted that if treatment is postponed unduly in experimental animals, recovery becomes more difficult. Hartman likewise reported that in the terminal stage of Addison's disease the use of cortical extract sometimes fails to bring about recovery, and he emphasized the development of an irreversible condition. The question of dosage, however, always enters into consideration in such a case, and if the massive doses reported by Kincov, Zillesen and Rowntree could be used more frequently, probably fewer failures would be reported.

Treatment in Cases of Complication with Acute Infection: The susceptibility to infection of the patient with Addison's disease and the importance of infection in the precipitation of a crisis have been emphasized. The slightest sign of infection is a peremptory indication for immediate intensive treatment with adrenal cortex extract. Six patients in this series died as a result of intercurrent infection, usually of the upper respiratory tract. In all these instances, the seriousness of the situation was not appreciated by the patient or his attendants. The initial infection was considered to be mild, and active therapy was postponed until too late. On the other hand, Rowntree, Greene, Swingle and Pfiffner have reported 1 instance (case 10) in which recovery from acute streptococcic sore throat, with bronchopneumonia, resulted from intensive therapy. Similar results were reported by Kenyon in a patient with diphtheria and by Cantor and Scott in a patient with acute bronchitis and subsequent acute cystitis.

Treatment in Cases in Which Operation Is Performed: Patients with Addison's disease are extremely poor risks from the surgical point of view. This condition can be modified by treatment, for several patients in this series had teeth extracted while they were receiving treatment; one patient underwent a minor operation on the nose, and

another, a plastic operation on the eyelid. These minor operations caused no more discomfort or reaction than if the patient had been in normal health—in striking contrast to the severe reaction which frequently characterizes such procedures in cases of Addison's disease in which no treatment is given. An additional case of Addison's disease in association with active tuberculosis of the testis and epididymis was reported by Greene, Walters and Rowntree. Epididymectomy and orchidectomy were done. Adrenal cortex extract was used in the preparation of the patient for operation and was administered as a postoperative measure. The patient made an uneventful recovery; but the tuberculosis was progressive, and two years later excision of the left kidney was successfully undertaken. Snell reported that the patient finally died of miliary tuberculosis.

Treatment in Cases of Partial Adrenal Insufficiency: The form of treatment best suited to a patient with Addison's disease who is not in crisis or who has been brought out of a crisis is a highly individual problem and must be determined in each case. Some patients, such as a man (case 14) in the present series, improve markedly while in the hospital and continue to take a small dose of adrenal cortex extract for two or three months after their discharge from the hospital. At the time of writing, the patient just mentioned reported that he had had no treatment since June 1931 and felt well. Roentgenograms showed an area of increased density in the region of the right adrenal, which suggested calcification. Another patient (case 5) likewise reported that she was in good health, though she had had no regular treatment for a similar period. In both these patients the pathologic process in the adrenals apparently was not progressive, and very few signs of adrenal insufficiency were shown. Adenoma-like islands of hypertrophied cortical cells are frequently observed in the adrenal glands in cases of Addison's disease. The functional activity of such regenerated tissue may explain the clinical improvement seen in cases such as the two just mentioned. Unfortunately, a case of this type represents the exception rather than the rule. More commonly, the patient regains a state of relative efficiency, whereby a moderate degree of activity can be maintained, with care and attention to the details of the daily life, a liberal intake of salt and fluids and supportive measures, such as have previously been advised after recovery from the initial crisis. Such patients, however, have little reserve, are readily upset and again pass into crisis. Recovery is possible with early and active treatment, though the initial vigor usually is not regained. Such patients require cortical extract only during the period of crisis, but experience has indicated that recovery is more rapid and complete if treatment is continued for a considerable period after each attack. Further, on the basis of clinical

evidence, the regular administration of small doses of the extract seems to be of value in maintaining the patient's resistance and so preventing the onset of the acute relapse or crisis. In cases of this type the beneficial effects of salt therapy and the use of a diet low in potassium are best seen. The successful management of a case of Addison's disease depends not on the choice of hormonal or of salt therapy but on the combination of the two to secure the best results.

In approximately a third of the cases in which my associates and I have made observations, the pathologic process apparently was active and the course of the illness progressively downward. Temporary improvement can be produced by intensive therapy, but, even at best, the patient's activities are extremely limited, and frequently he is confined to bed. Cantor and Scott reported such a case in which they made observations for twenty-six months, during which period there were fourteen distinct relapses and remissions. Eleven of these were experimentally produced by variations either in the dose or in the potency of the cortical extract which was used in therapy. Similar results were obtained in a patient (case 28) who was studied for a year in connection with clinical tests of different lots of cortical extract. At present, the status of patients who require the daily administration of cortical extract is truly pathetic, for few persons can afford to spend from $5 to $15 a day for medicine. In 2 cases in this series the patients deliberately discontinued treatment because of the expense. They died shortly afterward. Seven others were treated for varying periods, but in each case the inability to secure adequate supplies of cortical extract was a factor in the fatal outcome.

The effect of treatment in this series of 34 patients, who have been observed for periods up to six years, is indicated in the table. This table, constructed according to the method of Berkson, shows the total duration of the disease in relation to the percentage of survivors. It indicates that there was an increase in the duration of the disease in the series of treated patients. This increase in the duration of the disease in response to treatment, though slight, is greater than that observed in any other series of cases that has been reported.

The response to treatment is perhaps better shown in the accompanying chart. In this chart the cases are arranged on the basis of the duration of the disease before treatment was undertaken. For comparison with these values, the curve is shown to indicate the percentage of survivors in the series of patients summarized in the table who had no treatment. If the group of patients who were treated is taken as a whole, the duration of the disease before treatment was started corresponds approximately with the total duration of life of patients who received no treatment. In many instances the treatment added little to the apparent life expectancy of the patient. On the other hand. 11

of the 34 patients were under treatment for periods longer than the average duration of life of those who were untreated. Four are alive at the time of writing, and all of these persons started treatment more than five years ago. It is probable, therefore, that in a limited group of cases of Addison's disease treatment with salt and with cortical extract definitely increases the life of the patient.

Apart from the effect of treatment in the acute emergencies of Addison's disease and the apparent prolongation of life in selected cases, there are several effects of therapy that may be discussed separately.

Effect on Blood Pressure: The effect on blood pressure is slight, as compared with the other changes. When the patient is in shock,

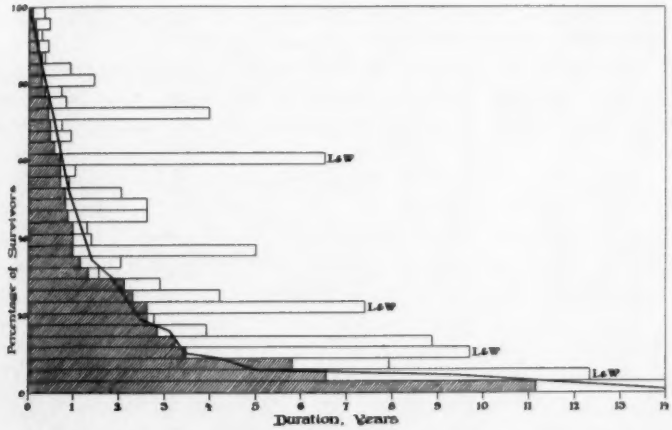

Chart showing the results of treatment in a series of 34 cases of Addison's disease. In this chart the areas of cross-hatching indicate the duration of the disease prior to treatment, and the plain areas, the duration of the illness after treatment. *L & W* means "living and well." One patient (case 22) was living and well in 1934 after being under treatment for four years. She moved away and has not been heard from since, so she is charted as having died at that time. The curve shows the percentage of survivors in a series of 266 cases in which no treatment was given.

the blood pressure may be very low, and, as the shock is effectively combated, the blood pressure rises, pari passu, to the lower level of normal. The systolic pressure then varies between 80 and 110 mm. Subsequent increases are slight and apparently are secondary to the general condition and the degree of activity of the patient.

Effect on Pigmentation: The degree of pigmentation in Addison's disease bears no direct relation to the severity of the disease, though it has been recognized that in the cases in which pigmentation is the

chief presenting symptom the subsequent clinical course may be slow and the disability slight. In some of the cases a marked decrease in pigmentation is shown after treatment is started. On the other hand, many patients respond well to treatment with adrenal cortex extract, and yet no change in the degree of pigmentation is noted.

Szent-Györgyi, in a brilliant series of chemical studies, isolated cevitamic acid from the adrenal cortex. It is now accepted that this substance is identical with vitamin C, the antiscorbutic vitamin. Administration of cevitamic acid is of no benefit to a totally adrenalectomized animal, but Szent-Györgyi expressed the belief that the substance plays a rôle in the formation of pigment and stated that its administration causes a decrease in pigmentation in Addison's disease. He therefore recommended a liberal intake of the citrous fruits as part of the diet of patients with this disease.

Effect on Weight: One of the striking effects of the administration of cortical extract is the disappearance of anorexia, nausea and vomiting; the patient again begins to take food, and normal intestinal activity is reestablished. With the taking of food there frequently is gain in weight. One patient gained 9½ pounds (4.3 Kg.) in eight days, and 3 patients, 10 pounds (4.5 Kg.) in one month. Other patients showed no change in weight. In general, one may state that the curve for weight follows the general condition and that gain is a good omen.

Effect on the Gonads: There is much evidence to suggest a physiologic relationship between the adrenal cortex and the gonads. In Addison's disease amenorrhea is a common symptom in women, while men complain of impotence. Several women in this series reported a return of regular menses while they were under treatment, and the men reported an increase in libido and potentia. Similar observations have been made by Hartman, Thompson and Russell, Neumann, Veran and others. Corey and Britton reported that the use of adrenal cortex extracts prepared by the method of Swingle and Pfiffner produces precocious sexual maturity in the albino rat, but Levy-Simpson, Kohn-Speyer and Korenchevsky were unable to confirm this observation. Until additional evidence is produced, the changes in sexual function in Addison's disease may be explained on the basis of the poor general condition of the patient, and the benefit derived from treatment may be ascribed to the improvement in the general condition of the patient as well as to specific stimulation of the gonads by the cortical hormone. The cortical hormone has not yet been identified conclusively. At least one of the crystalline fractions isolated from the adrenal gland is related, both chemically and physiologically, to the androgens, but the significance of this relationship is not yet understood. Pregnancy is an infrequent complication in Addison's disease, though Rowntree and Snell recorded 2 instances in their series. Perkins reported that a woman

with Addison's disease became pregnant after treatment with cortical extract was started. She was well during the pregnancy but passed into shock four hours after delivery. Recovery followed intensive therapy with cortical extract.

Effect of Oral Therapy: Britton, Flippin and Silvette reported that the oral administration of the cortical extract is effective in prolonging the life of completely adrenalectomized cats, and Grollman and Firor obtained similar results in dogs and rats. The dose, however, was from three to five times the dose required to produce comparable results when given parenterally. The question of expense at present precludes the oral use of cortical extract. On the other hand, the oral administration of dried adrenal cortex or of preparations such as the extracts employed by Rogoff and Stewart, Goldzieher or Hoskins and Freeman is a valuable adjunct to the injection of the cortical extracts. Grollman, Firor and Grollman recently have reported a simple preparation of the adrenal cortex that shows marked activity when administered by mouth. A preparation of proved efficiency such as this should have a wide field of usefulness in clinical medicine.

Effect of Overdosage: The clinical picture of tumor of the adrenal cortex is characteristic. This raises the question of possible harmful effects resulting from overdoses of the cortical extract. Toxic effects were occasionally noted after the administration of the extracts first prepared for clinical use. Similar effects have been reported by Benham, Fisher, More and Thurgar; Thompson and Whitehead; Herman, and others. These early reactions were apparently due to the presence of epinephrine or traces of protein in the extract, and they have not been observed with more highly purified preparations. I have seen no symptoms that could be ascribed to overdosage of the cortical extract either in normal persons or in patients with Addison's disease. Kincov, Zillessen and Rowntree gave enormous doses to a patient and reported no untoward reaction. Grollman and Firor likewise could show no effect in animals ascribable to an overdosage.

COMMENT

Numerous attempts have been made to determine the relative rôle of disturbances in the function of the cortical and of the medullary portion of the adrenal glands in producing the symptoms of Addison's disease. Harrop, for instance, suggested that hypotension, hypoglycemia and pigmentation are associated with disturbance of medullary function. Guttman reported that the duration of life is longest in cases in which pigmentation is the outstanding symptom and that cortical atrophy is seen more frequently than tuberculosis of the adrenals in cases of Addison's disease of a duration of five years or more. Guttman, however,

was unable to establish by statistical methods any distinct relationship between the symptomatology of Addison's disease and the type or the degree of involvement of the adrenals. The variability of the symptomatology is perhaps best explained if one considers the chemical componds which have been isolated from the adrenals and which are supposedly specific products—epinephrine, the lactyl epinephrine of Kendall and his associates and cevitamic acid. Finally, extracts containing the so-called cortical hormone have been prepared. Other products may yet be identified. Variations in the clinical picture of adrenal disease may well be explained by variations in the extent to which the production of these substances is disturbed. Recent work has shown that the so-called cortical hormone can be extracted in greater quantity from the whole gland than from the cortical portion, and it is possible that both the medulla and the cortex of the adrenal glands are concerned in the production of this hormone. Final decision is impossible at present, but if the cortical hormone is defined as the substance in the adrenal gland which is essential for maintaining the life of totally adrenalectomized animals, one may state that Addison's disease is due to deficiency in the supply of cortical hormone.

THERAPEUTIC USE OF ADRENAL CORTEX EXTRACT IN CONDITIONS OTHER THAN ADDISON'S DISEASE

Effects in Normal Persons.—I observed no definite response to the therapeutic use of adrenal cortex extract in normal persons. Weinstein and Marlow and Norlin and Skoglund confirmed this observation. Hartman, Greene, Bowen and Thorn, on the other hand, reported that in normal subjects injection of 1 cc. of extract usually produced some result and that from 3 to 5 cc. produced an unquestioned effect which lasted for several hours. Within an hour after the injection the subject was likely to feel sleepy, unless he was engaged in some activity which counteracted this effect. If he went to sleep, he slept soundly for an hour or so. Whether or not a nap was taken, the subject felt more active in the evening and seemed to be more alert and physically fit. The sense of well-being was noticeably increased. The night's sleep following the injection of extract of adrenal cortex was more sound, and the subject awoke the next day feeling more rested than usual. This effect on sleep was not observed by a good sleeper but was evident in the light sleeper. When the appetite was faulty, administration of extract of adrenal cortex seemed to stimulate it. Objectively, some subjects showed an increase in the power to do work, as recorded on the ergometer. This increase ranged from 50 to 500 per cent, the high point being reached a few days after the use of the extract was started. There seemed to be an increase in the reserve of energy of any subject

who had been nervous or tired. In 4 of the women the injection of from 3 to 5 cc. of extract of adrenal cortex daily for four or five days brought on menstruation from three to five days earlier than usual.

Conditions Associated with Shock.—The outstanding features of the clinical picture presented by a completely adrenalectomized dog and by a patient in an addisonian crisis are characteristic of the shock and anhydremia which are met in a variety of pathologic conditions in medical and surgical practice. This has led several investigators to conclude that these symptoms are due primarily or secondarily to a deficient supply of the cortical hormone (Zwemer, Harrop and Swingle and his associates). I am acquainted with 1 case of partial intestinal obstruction, with vomiting, dehydration and shock, in which marked improvement resulted from the use of cortical extract. Satisfactory therapeutic response to the use of cortical extracts in the treatment of shock due to acute intestinal intoxication in infants has been reported by MacLean, Sullivan and Zwemer, in cases of shock due to severe burn, by Hartman and by Wilson, Rowley and Gray and in surgical shock, by Rowntree.

Acute Infection.—The importance of the cortical hormone in increasing the resistance to infection of the patient with Addison's disease has been stressed. Robbins reported a case in which the condition was diagnosed as acute hypo-adrenalism, occurring as a sequela of acute streptococcic sore throat, and the disease responded to the administration of the extract of adrenal cortex prepared by the method of Hartman, while Hartman reported that the same extract was of value in the treatment of postinfectious asthenia. Neil, likewise, found the extract of value in the treatment of asthenia in a case of chronic bacteremia.

Bamberger and Wendt and Bernhardt have reported beneficial results in the circulatory insufficiency of diphtheria. I have seen an apparently specific response in cases of postinfluenzal asthenia. In these different conditions which seemed to respond favorably to the therapeutic use of adrenal cortex extract, exhaustion and muscular or cardiac asthenia were outstanding clinical symptoms.

Results are less sure in various other acute infections. Whitehead and Smith reported the use of cortical extract in the treatment of 1 patient each with typhoid, undulant fever, erysipelas, lymphangitis and sinusitis, with apparent improvement in all instances.

Wenner and Cone reported the use of cortical extract in 28 cases of pyogenic infection of the sinuses of the upper respiratory tract, with improvement in all instances. In these reports the decision with regard to the therapeutic effect of the extract was usually based on the subjective sensations of the patient. Under these conditions, it is difficult to determine the therapeutic effectiveness of a cortical extract.

Operation Involving the Adrenal Gland.—Tumor of the adrenal cortex produces a fairly definite clinical picture, and a few cases have been reported in which the tumor was removed successfully. The outcome is not always favorable, for in a considerable number of cases the patient passed into shock after the operation and died, with the clinical picture of acute adrenal insufficiency. These accidents have been explained by the hypothesis that hyperfunction of the tumor tissue produced hypofunction of the remaining normal gland and that normal function was not regained with sufficient rapidity after the operation to prevent the development of acute adrenal insufficiency. I have seen 1 such instance (subsequently reported by Walters, Wilder and Kepler, who have since reported 3 additional cases of this type) in which a diagnosis of hyperadrenalism was made. The surgeon removed a hypertrophied left adrenal gland, and two days after operation the patient passed into shock. Cortical extract was administered for five days, and the rest of the postoperative recovery was uneventful.

Prather also reported a similar case in which the patient passed into shock after the removal of a large hypernephroma and responded well to treatment with extract of the adrenal cortex.

Myasthenia Gravis.—The response to the administration of adrenal cortex extract was studied in 2 cases of myasthenia gravis. Hartman, Greene, Bowen and Thorn reported 3 cases, and Bernhardt and Levy-Simpson, 8 cases. Improvement was not continued in any of these patients, though Roch, Demole and Duchosal reported benefit in 1 instance.

Muscular Dystrophies.—Hartman has treated 6 patients with progressive muscular atrophy and 1 with muscular dystrophy with extract of adrenal cortex. The ultimate course of the disease was not influenced, though there was temporary increase in well-being. Mendelson, on the other hand, reported a case of progressive muscular dystrophy in which improvement with such treatment was marked. I treated a patient with diffuse myositis and profound muscular weakness, but with no benefit.

Disorders of the Thyroid Gland.—Possible interrelations between the function of the adrenal glands and that of the thyroid have been discussed at various times. Minnig reported that he obtained brilliant results with extract of adrenal cortex in the treatment of exophthalmic goiter, but he gave no details regarding the types studied or the results obtained. Bram reported similar subjective improvement in 12 cases of exophthalmic goiter in which the oral administration of a glycerin extract of the adrenal cortex was used in treatment. On the other hand, the effect of cortical extract was studied by my associates and me in 4 cases of exophthalmic goiter and by Hartman and his co-workers in a similar number, while Weinstein and Marlow reported 14 cases of exophthalmic goiter and 3 cases of adenoma of

the thyroid with hyperthyroidism. These investigators agreed that while in an occasional case subjective improvement might be shown, the metabolic rate was not affected and that there was no significant change in the clinical conditions.

There was no improvement in a case of myxedema in the present series in which treatment was given or in 2 cases of hypothyroidism reported by Weinstein and Marlow.

Effect on Asthenia.—The possible beneficial effect of adrenal cortex extract in various acute infections or of postinfectious asthenia has been discussed. In such cases there is pathologic and experimental evidence of disturbance of the adrenals. There is another group of cases in which at present the condition is variously diagnosed as neurasthenia, psychoneurosis or chronic exhaustion and in which physical and mental asthenia, with great fatigability, gastro-intestinal disturbance and vascular hypotension are marked. No definite pathologic changes in the adrenal glands have been reported in such cases, but functional adrenal insufficiency has been postulated by many clinicians. The cortical extract of Pfiffner and Swingle was used in 8 such cases in this study, but slight improvement was observed in only 1 instance. Hartman apparently obtained better results with his preparation of extract of adrenal cortex, for he reported temporary improvement in 10 of 16 cases studied. Leyton likewise reported marked improvement in suitably selected cases but gave no further details.

Vomiting of Pregnancy.—Kemp reported 14 cases of early vomiting of pregnancy in which relief was obtained by the oral administration of dried adrenal cortex. Freeman and Melick reported the injection of cortical extract in a case of pernicious vomiting of pregnancy with relief, while Hartman, Thorn and Potter reported a case of possible adrenal insufficiency, noted during pregnancy, in which there was a response to injections of cortical extract. Stemmer, Herbrand, Anselmino and Torre Blanco likewise reported the cortical extract of great value in treating vomiting or toxemia of pregnancy.

Asthma.—Fineman reported on the use of cortical extract in 4 cases of bronchial asthma. In 3 of these an increase in appetite and gain in weight occurred, but marked improvement in the severity of the asthma was observed in only 1 instance. Pottenger was enthusiastic about the beneficial results obtained by oral therapy in 50 cases of bronchial asthma. Cohen and Rudolph gave Rogoff's extract of adrenal cortex to 4 asthmatic patients without effect. The conflicting nature of these reports, the uncertainty regarding the composition and potency of the preparations used and the oral route of administration in most cases make it impossible at the present time to judge of the probable therapeutic value of cortical extract in asthma.

Miscellaneous Conditions.—I administered cortical extract in 4 cases of anorexia nervosa, with questionable benefit in 1 instance. Its use has also been tried in individual cases of diabetes, benign hypertension, postural hypotension and erythema nodosum, with no benefit. Questionable improvement was obtained in 1 case each of polyglandular deficiency and generalized tuberculous lymphadenitis. The latter condition, however, was possibly Addison's disease. Kalk reported a case of supposed hypophysial cachexia in which there was no response to pituitary therapy but in which the basal metabolic rate, the appetite and the weight increased after cortical extract was given.

Grüneberg reported improvement in 12 cases of psoriasis and in 1 of rheumatoid arthritis. Josephson reported beneficial effects in glaucoma and in hypertension. Essenson reported similar results in epilepsy and various other conditions. None of these reports were sufficiently detailed to permit the reader to make any objective judgment of the results obtained.

CONCLUSIONS

A series of 34 cases of Addison's disease in which treatment with salt and an extract of the adrenal cortex was used during the period from 1930 to 1937 is reported. The treatment added little to the apparent life expectancy in many cases but definitely prolonged life in a limited group of cases. The duration of the disease was more prolonged in this series of cases than has been reported with earlier methods of treatment.

Clinical experience has indicated that the effect of the administration of extract of the adrenal cortex is specific and limited in effect to Addison's disease or to other conditions in which there is reason to suspect acute adrenal insufficiency. In general, this response has been so specific as to suggest that the therapeutic trial constitutes a reliable diagnostic test, an opinion which was seconded by Geill.

The recorded experience of other observers in general is in agreement. Hartman and his collaborators have reported some benefit in a wider variety of conditions than is indicated in my experience. That adrenal insufficiency in its broadest aspects involves a variety of active principles has already been pointed out. Variations in the composition of various extracts may well explain some of the differing results obtained by their clinical use. The isolation of these principles in pure state by chemists apparently will soon be attained. This leads one to hope that it will not be long before these substances are made available to the physician at reasonable cost. Once this is done there is reason to hope for a better understanding of the rôle of adrenal insufficiency in medicine and of the clinical indications for the therapeutic use of extract of the adrenal cortex.

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INFLUENCE OF GASTRIC ACIDITY AND DEGREE OF ANEMIA ON IRON RETENTION

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We have shown in a previous report [1] that patients with hypochromic anemia retain large amounts of iron when the doses of iron and ammonium citrates are administered by mouth. The results were obtained with the administration of 3 Gm. of iron and ammonium citrates per day and were not appreciably influenced by the gastric acidity or the severity of the anemia. The present communication deals more specifically with the effect of these particular factors on the retention of iron when varying amounts of the metal are administered.

It has been shown that iron is absorbed from the duodenum and the upper portion of the jejunum.[2] Lintzel [3] stated as his belief that it is absorbed only in an ionized form and that an acid reaction is necessary for this ionization, and Verzar,[4] among others, has expressed a similar view. Mettier and Minot [5] have shown by means of the reticulocyte response that a better utilization of a small amount of iron is obtained when it is given in an acid medium, but with large amounts a satisfactory response of the bone marrow will ensue, even though the drug is given in an alkaline solution.

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The iron balance of fifteen patients with achlorhydria and eleven with normal or low gastric acidity were studied in an attempt to ascertain the effect of gastric acidity on the retention of iron. All the patients with free hydrochloric acid in the gastric contents, even though it was present only after the administration of histamine, were included in the latter group. The balance studies were preceded by a three day period of adjustment before observations were begun. The balance periods were six days long, and the beginning and end of each was marked by the administration of carmine. The method of study, the technical procedures and the precautions against contamination were given in a previous paper.[1]

TABLE 1.—*Achlorhydria*

Patient	Gastric Acidity	Daily Iron Intake, Mg.	Daily Iron Balance, Mg.	Hemoglobin, Gm. per 100 Cc.	Diagnosis
1	0	10.03	— 0.71	7.89	Idiopathic hypochromic anemia
2	0	9.13	—10.77	8.10	Hemorrhage
3	0	9.96	—11.05	7.71	Anemia of pregnancy
4	0	10.26	— 7.12	12.17	Steatorrhea
5	0	9.72	— 7.83	4.58	Idiopathic hypochromic anemia
6	0	11.88	— 3.15	5.55	Idiopathic hypochromic anemia
7	0	13.14	+ 1.24	12.51	Idiopathic hypochromic anemia
8	0	11.89	— 9.78	4.78	Idiopathic hypochromic anemia
9	0	11.49	+ 2.27	7.89	Lead poisoning
10	0	10.17	— 4.28	7.45	Hemorrhage
11	0	11.89	+ 3.01	2.36	Hemorrhage
Average.....		10.86	— 4.379		

TABLE 2.—*Normal or Low Gastric Acidity*

Patient	Gastric Acidity	Daily Iron Intake, Mg.	Daily Iron Balance, Mg.	Hemoglobin, Gm. per 100 Cc.	Diagnosis
1	Normal	10.12	—2.10	10.20	Hemorrhage
2	Normal	11.96	+2.20	6.25	Hemorrhage
3	Normal	12.51	+1.39	7.45	Hemorrhage
4	Normal	12.27	+2.66	4.07	Idiopathic hypochromic anemia
5	Normal	13.43	—1.19	12.91	Diabetes
6	Normal	9.69	—2.62	10.71	Diabetes
7	Normal	11.81	+3.45	12.62	Arthritis
8	Normal	11.78	+2.64	11.99	Arthritis
9	Low	9.98	—9.91	4.36	Hemorrhage
10	Low	12.57	+2.91	5.65	Idiopathic hypochromic anemia
11	Low	12.25	+1.67	6.66	Idiopathic hypochromic anemia
12	Low	11.96	+4.64	8.45	Idiopathic hypochromic anemia
13	Low	11.78	—1.63	11.78	Diabetes
14	Low	12.85	+6.30	10.81	Diabetes
15	Low	12.85	+4.89	12.05	Diabetes
Average.....		11.85	+1.02		

The daily intake of iron and the iron balance, the hemoglobin content of the blood in grams per hundred cubic centimeters, and the diagnosis in each case are given in tables 1 and 2. The ingested iron, obtained from food alone, varied from 9.13 to 13.14 mg. per day. For the patients with achlorhydria the intake of iron averaged 10.86 mg. per day and for those with free hydrochloric acid 11.85 mg. Eight, or 72.8 per cent, of the patients with achlorhydria showed a negative iron balance on this diet, and the average daily iron balance for the group was —4.379 mg. In the group of patients with free hydrochloric acid only five, or 33.3 per cent, showed a negative iron

balance and ten, 66.6 per cent, a positive balance. The average daily iron balance was + 1.02 mg. This difference between the average daily iron balances for the two groups indicates that achlorhydria diminishes the absorption of dietary iron. This finding is supported by the fact that 72.8 per cent of the patients with achlorhydria showed a negative iron balance, as compared with 33.3 per cent of those having hydrochloric acid in the gastric contents.

If the group of patients with achlorhydria is further subdivided so as to compare the iron balances for those with an idiopathic form of anemia with the balance for those with anemia secondary to a chronic loss of blood, it is found that the average daily iron balance for the five patients with idiopathic hypochromic anemia was —4.04 mg., whereas that for the remaining six patients was —4.65 mg. This variation is too slight to be of significance and demonstrates the fact that there is no appreciable difference in the absorption of iron by the patients with idiopathic anemia and that by those with post-

TABLE 3.—*Average Daily Iron Balance; Effect of Added Hydrochloric Acid*

	Achlorhydria		Hydrochloric Acid Added	
Patient	Daily Iron Intake, Mg.	Daily Iron Balance, Mg.	Daily Iron Intake, Mg.	Daily Iron Balance, Mg.
1	14.19	+7.33	12.48	+8.47
2	14.07	+7.12	13.13	+2.48
3	12.67	+2.23	12.79	—5.67
4	11.91	—4.22	12.21	—3.42

hemorrhagic hypochromic anemia when achlorhydria is present in both. We have previously shown that with the administration of large amounts of iron by mouth the patients with idiopathic hypochromic anemia retain and utilize as much iron as do patients with other types of hypochromic anemia. Although faulty iron metabolism has been mentioned as a possible etiologic factor in these cases, our observations do not support this hypothesis.

It has been suggested by previous investigators that the addition of hydrochloric acid increases the absorption and utilization of iron. Table 3 gives the results obtained in four patients for whom the iron balance was studied without additional acid by mouth and again with the addition of hydrochloric acid and pepsin. These patients received 200 cc. of tenth-normal solution of hydrochloric acid and 0.5 Gm. of pepsin three times daily with their meals. Patients 1 and 2 of this group were not anemic. Neither patient had free hydrochloric acid before the administration of histamine, but both responded to this stimulation by secreting small amounts of acid. Patient 1 retained 7.33 mg. of iron and with the addition of acid and pepsin retained 8.47 mg. per day. The daily intake of iron in the food was slightly less

during the latter period. Patient 2 retained 7.12 mg. of iron per day but with the addition of hydrochloric acid retained only 2.48 mg. Patient 3, with idiopathic hypochromic anemia and hypochlorhydria, was subjected to the same procedure, and in spite of a slightly increased intake of iron during the period of the administration of acid, the daily iron balance dropped from +2.23 to —5.67 mg. Patient 4, with idiopathic hypochromic anemia and achlorhydria, showed only a slight increase with the addition of acid, the daily iron balance increasing from —4.22 to —3.42 mg. per day. The balance periods in these experiments lasted for twelve days, except for the second period in patient 1, which was only six days. These experiments show two patients with a slight increase in the retention of iron after the administration of hydrochloric acid and two with a definitely lowered retention after the same procedure. The results are presented as evidence that the addition of hydrochloric acid, even in excess of the usual therapeutic dose, does

TABLE 4.—*Average Daily Iron Balance (by Periods) with a Daily Intake of 500 Mg.; Effect of Added Hydrochloric Acid on Retention of Iron*

	Control Period	Period 1	Period 2	Period 3	Period 4
Average daily balance of ten patients presented in previous paper	—4.80	217.93	225.70	202.75	143.49
Average daily balance of three patients with achlorhydria receiving no additional hydrochloric acid	—5.31	238.48	200.24	351.61	386.30
Average daily balance of four patients with achlorhydria but receiving hydrochloric acid	—9.88	189.00	231.73	293.34	200.57

not significantly increase the retention of iron in a patient with achlorhydria receiving a normal dietary intake of iron.

Although hydrochloric acid had no significant influence on the retention of iron under these conditions, its effect was studied in patients receiving large amounts of iron. Table 4 gives the retention of iron by periods for patients receiving approximately 500 mg. of iron per day in the form of iron and ammonium citrates. This table includes the average retention of iron in ten patients presented in the preceding paper.[1] It is to be noted that the average daily retention of iron in the patients with achlorhydria who did not receive hydrochloric acid was slightly greater, except for the second balance period, than the average retention for the entire group. When this same group of patients with achlorhydria is compared with a group receiving hydrochloric acid and a similar amount of iron, it is seen that those without the additional acid retained more iron, except in the second balance period, than did those receiving acid. The differences in the amount of iron retained are not great but are sufficient to indicate that with a large intake of iron achlorhydria does not appreciably diminish the

retention of iron and that the addition of hydrochloric acid does not significantly increase the amount retained.

To substantiate further the interpretation placed on the foregoing results, the studies of the iron balance of two patients with achlorhydria who received 3 Gm. of iron and ammonium citrates per day are presented in table 5. Patient 1 retained 225.3 mg. of iron per day, and with the same intake of iron but with the addition of 60 minims of tenth-normal hydrochloric acid to each dose of iron and ammonium citrates she retained 225.15 mg. per day. A second patient had a daily retention of 76.41 mg. of iron per day for twelve days, but with the addition of hydrochloric acid only 64.83 mg. was retained per day.

TABLE 5.—*Average Daily Iron Balance with a Daily Intake of 500 Mg.*

	Iron Balance, Mg.		
Patient	During Control Period	During Achlorhydria	With Addition of Hydrochloric Acid
1	—10.77	+225.30	+225.15
2	+17.90	+ 76.41	+ 64.83

TABLE 6.—*Average Daily Iron Balance (by Periods) with a Daily Intake of 500 Mg.; Effect of Hemoglobin Content on Retention of Iron*

	Control Period	Period 1	Period 2	Period 3	Period 4	Period 5
Average daily balance of ten anemic patients [1]	—4.80	+217.93	+225.70	+202.75	+143.49	+ 69.13
Average daily balance of five nonanemic control subjects	+2.87	+282.15	+188.31	+243.12	+220.65	+147.12
Average daily balance of five patients with lowest hemoglobin values	—4.94	+174.62	+176.42	+172.99	+ 82.79	+ 69.30

It has been stated that an anemic organism leans toward retention of iron,[6] and animal experiments have demonstrated that a dog rendered progressively more anemic by repeated hemorrhages eliminates smaller and smaller amounts of iron while on a constant intake of iron.[7] With the depletion of the stores of iron in the body an increased avidity for iron might be anticipated. Table 6 presents data bearing on this question. The average daily retention of iron by five nonanemic subjects was greater during four of the five balance periods than was the average retention of ten anemic persons with the same intake, 500 mg. of iron per day. When five nonanemic subjects were compared with

6. Müller, A. H.: Die Bedeutung des Eisens bei Anämien: Die Eisenbilanz sekundärer Anämien unter dem Einfluss der Lebereisentherapie, Ztschr. f. d. ges. exper. Med. **91**:585, 1933.

7. Fontès, G., and Thivolle, L.: Elimination du fer et anémie expérimentale, Sang **6**:445, 1932.

the five patients with the lowest hemoglobin content, it was seen that those with a normal hemoglobin value consistently retained more iron. These data are interpreted as indicating that there is no correlation between the hemoglobin level and the absorption of iron when it is administered in large amounts.

A similar conclusion can be drawn from a further consideration of data in table 2. In eight of the patients whose gastric content contained free hydrochloric acid the hemoglobin level was only slightly reduced. The average daily iron balance of these patients on a normal dietary intake of iron was + 1.21 mg. per day, while the balance for seven anemic patients on the same diet was + 0.79 mg. per day. A difference of 0.42 mg. per day is not significant, but the trend is in the same direction as that for patients receiving large amounts of iron. Since similar results were obtained under these different circumstances, it seems apparent that a low hemoglobin level does not increase the retention of iron.

Attempts have been made for many years to determine the normal iron requirement of man, and the recent widespread interest in the subject of hypochromic anemia has acted as an added stimulus to this investigation. Reviews of previous experimental work have been given recently.[8] Lintzel [8] has stated that a very small amount of iron is required by human beings and that a man weighing 70 Kg. can be in iron balance with an intake of 1 mg. per day. He stated that if a diet with a constant iron content is given, the body soon establishes a rate of excretion of iron which agrees with the intake and a balance is established. If the diet is increased so as to contain larger amounts of iron, the body again becomes in balance within two days. Farrar and Goldhamer [8b] studied four patients who had been receiving a constant amount of iron (from 4.9 to 9.1 mg. per day) for periods ranging from forty-one to three hundred and sixteen days and found all the patients to be in equilibrium. The hemoglobin content and the erythrocyte counts were normal at the end of this period, and they concluded that the daily requirement of iron is not more than 5 mg. Ohlson and Daum,[9] however, in studying three normal women with an average daily intake of 13.78 mg. of iron, found the excretion to be 14.95 mg. per day, a negative balance of 1.17 mg.

We have determined the iron balance for four women, two with anemia and two with normal hemoglobin and erythrocyte values, during periods of a low and of a normal intake of iron. These diets contained

8. (*a*) The Iron Requirement of Man, editorial, J. A. M. A. **105**:1917 (Dec. 7) 1935. (*b*) Farrar, G. E., and Goldhamer, S. M.: The Iron Requirement of the Normal Human Adult, J. Nutrition **10**:241, 1935.

9. Ohlson, M. A., and Daum, K.: A Study of the Iron Metabolism of Normal Women, J. Nutrition **9**:75, 1935.

from 3.81 to 6.67 mg. of iron per day, although considerable difficulty was encountered in planning a palatable diet of low iron content. It will be seen from table 7 that all the patients on the diet low in iron were in negative iron balance, varying from —1.22 to —5.15 mg. per day. Four of these patients were then placed on a diet with a normal iron content, and all of them returned to a positive balance. These balance periods were from twelve to eighteen days long. The consistently negative balance with the diet low in iron suggests that the daily requirement of these subjects was in excess of 5 mg. and does not agree with Lintzel's statement that the body adjusts itself to a state of balance after two days of a given intake of iron.

With the consistently negative iron balance in patients on a low intake of iron, it is possible that such diets might lead to a deficiency of iron and to anemia in certain cases, but from the difficulty encountered

TABLE 7.—*Effect of Diets with Low and Normal Amounts of Iron on Iron Retention*

	Diet Low in Iron		Diet with Normal Amount of Iron	
Patient	Daily Iron Intake, Mg.	Daily Iron Balance, Mg.	Daily Iron Intake, Mg.	Daily Iron Balance, Mg.
1	6.67	—5.15	14.19	+7.33
2	6.74	—4.79	14.07	+7.12
3	5.29	—2.05	13.14	+1.24
4	4.14	—2.90	12.27	+2.66
5	5.72	—1.22		

in planning a diet low in iron and from a comparison of this diet with that which had been regularly eaten by our patients with idiopathic hypochromic anemia, we do not feel that it is a frequent cause of such anemia.

COMMENT

These experiments show that patients with achlorhydria retain less iron from a normal dietary intake of iron than do patients with free hydrochloric acid in the gastric contents. This was evidenced by the average iron balance in the two groups as well as by the number of patients in negative balance. It is apparent that this diminished retention of iron may play a part in the etiology in certain cases of idiopathic hypochromic anemia, although we do not believe it to be the only etiologic factor.

Our results show that with a large intake of iron (500 mg. per day) the retention of iron is not influenced by the gastric acidity and that the administration of hydrochloric acid, even in large amounts, does not increase the retention of iron. The latter was true both with normal

and with large amounts of iron and indicates that the administration of hydrochloric acid is not necessary for an adequate retention of iron.

The previous experimental evidence that an anemic organism has an increased avidity for iron and retains its iron with greater tenacity is none too conclusive, and the results of our experiments on human beings do not substantiate this contention. Nonanemic subjects retained as much iron as did patients with anemia from a normal intake of iron as well as when large amounts of iron were administered. One might expect the reverse to be true when the reserve stores of iron are depleted by chronic hemorrhage, but no evidence of this was obtained.

There is much conflicting evidence in regard to the iron requirement of normal subjects, but recent work has indicated that it is lower than was formerly believed. Farrar and Goldhamer stated their belief that it is not over 5 mg. per day. Our results are at considerable variance with theirs, since five patients on a low intake of iron, 3.81 to 6.67 mg. per day, were all in negative balance and four of these patients who were placed on a diet with a normal content of iron subsequently showed a positive balance. This indicates that an intake of 6.7 mg. per day is not sufficient for the needs of these patients; but as we were not dealing with normal subjects, these results are not strictly comparable to those obtained in healthy subjects.

SUMMARY

Achlorhydria decreases the retention of iron from a normal dietary intake of iron but does not influence the retention when large amounts of iron are administered by mouth.

The addition of hydrochloric acid does not increase the retention of iron with either a high or a normal intake of iron.

The presence of anemia does not influence the amount of iron retained.

A dietary intake of iron of 6.7 mg. per day is not sufficient to keep these patients in iron balance.

GENERALIZED XANTHOMA TUBEROSUM WITH XANTHOMATOUS CHANGES IN FRESH SCARS OF AN INTERCURRENT ZOSTER

ADENOCARCINOMA OF THE AMPULLA OF VATER AT NECROPSY

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AND
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PHILADELPHIA

As to the several phases indicated in the title, there is no surprise at the development of xanthomatous characteristics in a zoster lesion since zoster is only one member of the list of diseases the sequelae of which may be fibrous; almost a dozen cases of "scar xanthomas" have already been described in the literature. Nevertheless, this additional illustration of the notorious propensity for xanthomatous infiltration to involve granulation tissue amplifies the knowledge of the conditions under which the infiltration can take place. It is thoroughly established that hypercholesterosis of itself will not guarantee xanthomatous infiltration even in the presence of pathologic fibrous tissue. There are an additional *x* and perhaps also *y* and *z* factors in the pathogenesis that remain to be sought out. Before one can generalize, one needs more and more data covering both the local and the general conditions under which xanthomas develop in scars, and we feel that our case adds one more item to the accumulation.

As to the association with cancer, this was at the time of its observation almost unique; however, Weidman and Schaffer [1] have recorded another instance—this time in cancer of the stomach—which focuses attention on still another avenue for xanthomatosis and which may perhaps revive interest in the cholesterol-cancer interrelationships. Xanthosarcoma, it is true, is another malignant process involving a joining of xanthomatosis and a malignant process, but here the situation is different, because the two processes are combined in the same cell and do not appear as separate lesions. The carcinomatous phase in our case is especially pertinent because it raises the question of a particular factor,

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1. Weidman, F. D., and Schaffer, H. W.: Xanthoma of the Skin and Larynx, Associated with Carcinoma of the Stomach and Regressive Xanthoma of the Pons, Arch. Dermat. & Syph. **35**:767 (May) 1937.

namely, cancer, in the development of the hepatic disease of which xanthoma has long been established as a notorious sequel. The extremely high cholesterol value (1,020 mg. per hundred cubic centimeters) is also illuminating, if only from the abstract quantitative standpoint.

If it is admitted that the cancer was the primary factor in the chain of events leading to the xanthoma, this case also shows to what extreme the dermatologist may have to carry his internal medical studies if he would exhaust every possible etiologic possibility in a given case of generalized xanthoma tuberosum.

There is an additional, practical angle to our experience in that an exploratory laparotomy was performed, directed at biliary obstruction; surgery has been drafted but seldom in the therapeutic approach directly to the exciting etiologic factor in a xanthomatous process. The performance of a necropsy on our patient added much to the value of this report; it should stimulate more complete studies of xanthomatous patients in the future.

The prominence of the English in the field of necropsy, even during the era of Virchow, provokes thought as to whether xanthomatous changes are particularly common in England, and, if so, whether English habits of diet and drinking are (or at least were) conducive to this essentially metabolic disease. The creation of the English Xanthoma Committee (Hutchinson, Sangster and Crocker [2]) points convincingly to the importance of the disease at that time.

REPORT OF A CASE

History.—Michael M., a white man aged 44, an ice cream maker, named as his first symptom (August, 1926) a generalized pruritus. Four weeks later, jaundice developed. At this time the stools were of the color of clay, but they promptly returned to yellow.

The xanthomatous nodules developed five months after the onset of the pruritus. They were characteristically distributed on the elbows, knees and rims of the ears and at the angles of the mouth. In contrast to most cases of xanthoma tuberosum, the palms were affected (but without inflammatory areolae as in diabetes), the lesions being concentrated particularly along the deeper creases. Widely scattered lesions occurred on the back, buttocks and extensor surfaces of the arms. At the vertex of the skull there were several large, depressed scars; on roentgen examination the outer plate was found markedly rarefied. The patient claimed that the scars were the result of an old accident, but in view of the presence of certain other scars on the arms and shins, together with a positive Wassermann test of the blood, it was concluded that they were part of an old syphilitic process.

One of the eyes exhibited a large macule of the cornea with irregular refraction throughout the entire cornea. A good view of the fundus could therefore not be obtained. Within eight months the patient lost 35 pounds (15.9 Kg.)

2. Hutchinson, J.; Sangster, A., and Crocker, H.: Report of Xanthoma Committee, Tr. Path. Soc. London **33**:376, 1882.

The routine detailed physical examination did not disclose abnormalities of the viscera except marked enlargement of the liver (it extended 8 cm. below the costal border in the midaxillary line). Accordingly, the gallbladder was drained on three occasions (nine months after the onset of the disease), and from 12 to 16 ounces (354 to 473 cc.) of fluid was removed.

The Zoster Lesion.—The lesion developed on April 21, 1927, eight months after the onset of the disease, on the left side of the chest along the distribution of the seventh, eighth and ninth thoracic nerves. It was quite characteristic. The xanthomatous changes were observed in it one month later. Some of the papules were red at that time, but on pressure showed a yellowish cast. However, other papules were definitely yellow even without pressure. At this time, a group of minute, punctate yellowish papules was also observed immediately below the lower lip. They had a follicular distribution; i. e., they were uniformly spaced, suggesting that the follicular orifices might have been traumatized as the result of close shaving, and that xanthomatous changes had developed in the microscopic scars which resulted.

Fig. 1.—Classic location of xanthoma tuberosum on the elbows. The forearms are freckled.

Roentgenologic Examination.—The sella turcica appeared to be normal. The outer plate of the skull at the vertex was rarefied. The gallbladder was not visualized in the twelve or fourteen hour period. The stomach, duodenum, tibia and humerus (metastatic lesions?) were normal.

Laboratory Examinations.—Several examinations were made of the urine. The specific gravity ranged between 1.008 and 1.015. A trace of albumin was observed several times; leukocytes and epithelial cells were sparingly found on one or two occasions. There was no sugar.

The feces did not show blood or parasites.

Hematologic Studies: The red blood cells numbered 2,910,000, and the leukocytes, 16,200 and 19,000. The hemoglobin measured 9.7 Gm.

Blood Chemistry: The dextrose measured 100 mg., and the urea, 11 mg., per hundred cubic centimeters. The van den Bergh reaction was positive on the

immediate test; the icteric index was 45. The coagulation time was four and a half minutes; the bleeding time, two and a half minutes. The Wassermann test of the blood was at first positive, but later negative. The blood cholesterol measured 960 and 1,020 mg. per hundred cubic centimeters on two different occasions, yet the serum was not milky.

Electrocardiographic study gave a normal tracing.

Biopsies were performed three times (May 7, Aug. 30 and Nov. 28, 1927); twice at an earlier stage of the xanthomatosis and once later, after the zoster had developed. In the first specimen examined, classic xanthoma cells appeared; they were confined to the uppermost parts of the corium, crowding the papillae, abutting directly on the basement membrane above and extending around blood vessels in the subpapillary region and slightly deeper. There were no giant cells.

In the second specimen taken for biopsy (from the elbow), the processes were found to be regressive; i. e., the epiderm had become denuded, probably as the

Fig. 2.—Linear distribution of xanthomas on the palms; inflammatory areola such as occurs in diabetic xanthoma was absent.

result of traumatism, and the foamy quality of the cytoplasm could be only vaguely recognized. The xanthomatous areas appeared as an indifferent pink granular matrix, interspersed with distorted spindle cells. Evidently the nuclei of the xanthoma cells, although once compromised as to vitality, were returning to an approximately normal state. If this is true, in so doing they indicated their original nature; i. e., they were spindle cells rather than cells of the reticuloendothelial system.

At the third biopsy both an older lesion from the elbow and a recent one from the healed zoster (now xanthic) were examined. The observations on both the lesions were the same as those of the first biopsy, except for a notable polymorphonuclear infiltration around the hair follicles in the zoster lesion. This should not be referred to unabsorbed infiltrate from the zoster, because the patient also had an abscess of the lobe of the ear at this time, and had, in fact, complained a number of times about the development of pustules in xanthomas elsewhere—on

the fingers, for example. Singularly, only the xanthoma cells in the subpapillary regions stained with sudan III in frozen sections; deeper ones did not take the dye. Crystalline forms (rods) and cholesterol crystals were not recognizable. It should be remembered that the zoster lesion was a comparatively acute example of xanthomatous change (seven months' duration).

Pus from the ear, stained by Giemsa's stain, showed that nearly all of the leukocytes were eosinophils. There were many intracellular diplococci.

As fats in subcutaneous tissue had been successfully stained with carotene,[3] this substance was tested on frozen sections of xanthoma lesions. In no case did the fat become colored until sections had been heated. Thereupon, the fat globules coalesced; it was then possible to make out a faint yellow coloration in the larger globules but not in the smaller ones.

Fig. 3.—Xanthomas in zosteriform distribution.

Clinical Diagnosis. —The clinical diagnosis was xanthoma tuberosum multiplex, hypertrophic biliary cirrhosis of the liver, malignant degeneration, herpes zoster and syphilis.

Exploratory Laparotomy.—Nineteen months after the onset of the disease, exploratory laparotomy was performed, directed toward possible biliary obstruction. It was recognized that the cystic duct was enlarged to the size of an average thumb, and that the head of the pancreas was indurated; however, biliary obstruction could not be demonstrated. Small deposits in the wall of the large and small bowel were considered to be deposits of cholesterol. The patient died on the operating table from cardiac failure.

3. Weidman, F. D.: Carotin as a Specific Fat Stain, as Demonstrated in Frozen Sections, Proc. Path. Soc. Philadelphia, 1927, p. 24.

Necropsy.—Necropsy was performed forty-eight hours after death. All of the organs and tissues were deeply jaundiced. The gallbladder exhibited a mild chronic inflammation; it was thick walled and small, and had collapsed. It contained no stones, but its lining was deep red and incrusted by bile-stained, chalky material. The bile was pale, intermixed with about 5 cc. of a deep green amorphous substance. All of the bile ducts were definitely dilated, had thickened fibrous walls and were lined by bright yellow granular incrustive material. There was definite narrowing at the papilla of Vater; however, it was possible to pass a probe into the biliary passages. The common duct immediately above the papilla

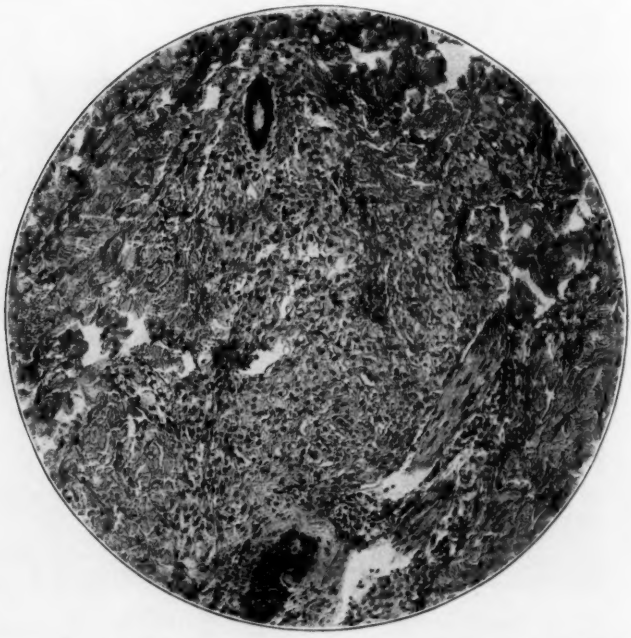

Fig. 4.—Focus of xanthoma cells in relation to pilosebaceous apparatus (biopsy specimen taken from the skin).

of Vater was particularly dilated (3.5 cm. in circumference). Formation of tumor could not be demonstrated; the indurative processes were regarded as being chronic inflammatory.

The liver was enlarged, weighing 2,820 Gm. It was deeply jaundiced, but had a much more smooth surface than was expected. Otherwise, it had the characteristics of biliary cirrhosis. The linings of the intrahepatic bile ducts were encrusted with bile-stained chalky material similar to that encountered in the gallbladder.

The kidneys were enlarged, weighing 200 Gm. each. The conspicuous feature in them was the yellow streaking in the pyramids, reminding one of the streaks of uric acid in gout.

The adrenal glands were small. They had an extremely narrow cortex, and the yellow lipoidal substance was present only in restricted parts.

There were one or two plaques of bright yellow atheroma on the lining of the left auricle. The valves were comparatively normal; there were no signs of syphilis anatomically in either the heart or the aorta. The aorta showed, likewise, a few plaques of atheroma, some with hyaline changes in addition. The changes were not, however, of syphilitic type. It is emphasized that, besides a very early atheroma, there were separate and distinct brighter yellow deposits scattered through the entire length of the aorta. The same was true of the pulmonary arteries.

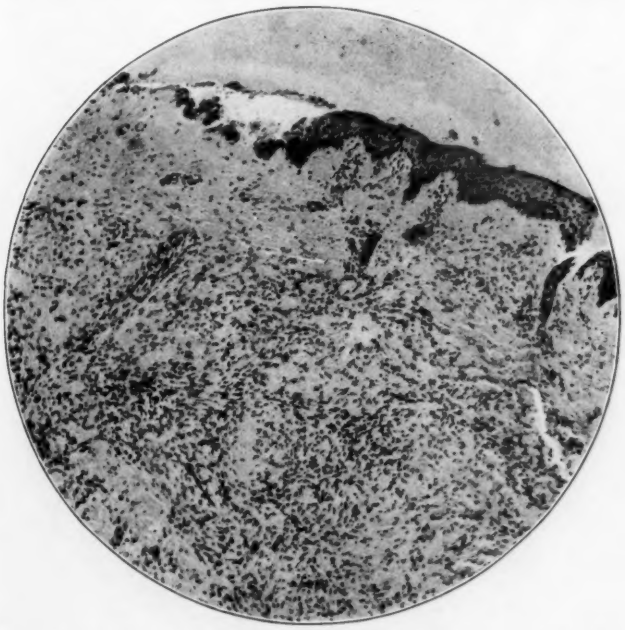

Fig. 5.—Regressive lesion on the elbow. Only spindle cells remain; there are no xanthoma cells. The epiderm over this very old lesion was largely destroyed by traumatism.

The spleen was large and covered with hyaline plaques. In addition, there were numerous thin flat bright yellow deposits on the capsule.

The pancreas was somewhat hard, but otherwise normal.

The esophagus, stomach and large and small intestines appeared normal except for an occasional yellowish patch in the intestinal wall, such as the surgeons had recognized at operation.

All of the internal lymph nodes were definitely enlarged, averaging 1 cm. in diameter. They were soft and edematous, and many of them showed small bright yellow areas similar to those found on other organs.

The testicles, epididymis, seminal vesicles, prostate and prostatic urethra appeared normal.

The thyroid gland appeared normal.

The peripheral arteries were mildly atheromatous.

The brain was of such soft consistency that its substance had a tendency to fall away (the autopsy was performed forty-eight hours after death). The dentate nuclei were severely sclerotic.

Gross Anatomic Diagnosis.—The heart showed slight hypertrophy, cloudy swelling and jaundice. There were deposits of cholesterol in the endocardium. The left lung showed partial collapse of the lower lobe. There was slight congestion of both lobes. The right lung showed congestion and jaundice. The spleen presented diffuse hyperplasia and deposits of cholesterol in the subcapsular tissue.

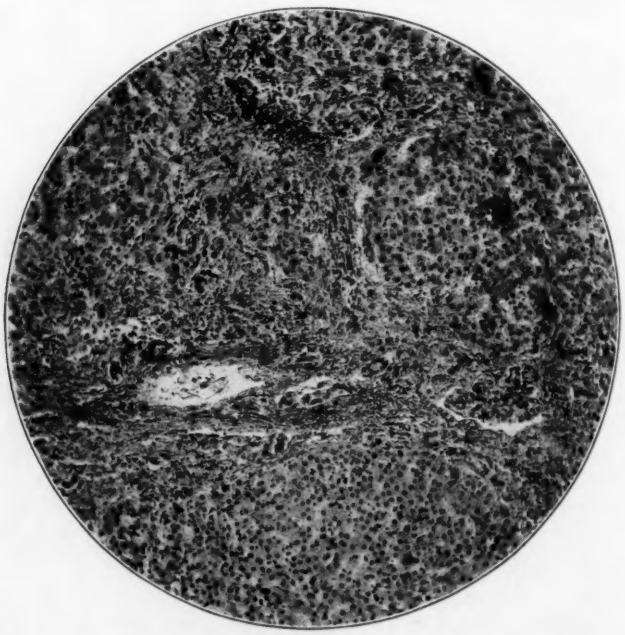

Fig. 6.—Hypertrophic biliary cirrhosis of the liver. Parenchymal cells do not exhibit cramming of cholesterol.

The kidneys were jaundiced and showed old infarcts, cloudy swelling and deposits of cholesterol in the pyramids (?). The liver showed hypertrophic biliary cirrhosis. The biliary system showed dilatation of all ducts with deposits of cholesterol in the mucosa. There was chronic inflammation of the papilla of Vater. There were deposits of cholesterol in the intima of the aorta. The lymphatic system showed hyperplasia and deposits of cholesterol (?). The brain showed marked general edema, with congestion. There was severe sclerosis of the dentate nucleus.

Histologic Examination.—In addition to sections embedded in paraffin and stained by hematoxylin and eosin, frozen sections stained with sudan III were made

from the liver, kidney, adrenal glands, spleen and aorta, i. e., the organs which were expected to show fatty changes.

The lungs showed no evidence of xanthomatous change or metastatic cancer. Areas of collapse and fibrosis, with small foci of calcification of the bronchial cartilages, comprised the pathologic features.

The muscle fibers of the heart were narrow and coarsely granular; the transverse markings were invisible. There were no xanthomatous changes.

Sections of the liver stained with hematoxylin and eosin confirmed the gross diagnosis of a high (but not extreme) grade of biliary (not Hanot's) cirrhosis. Bile ducts and fibrous tissue of Glisson's capsule were moderately hyperplastic, and

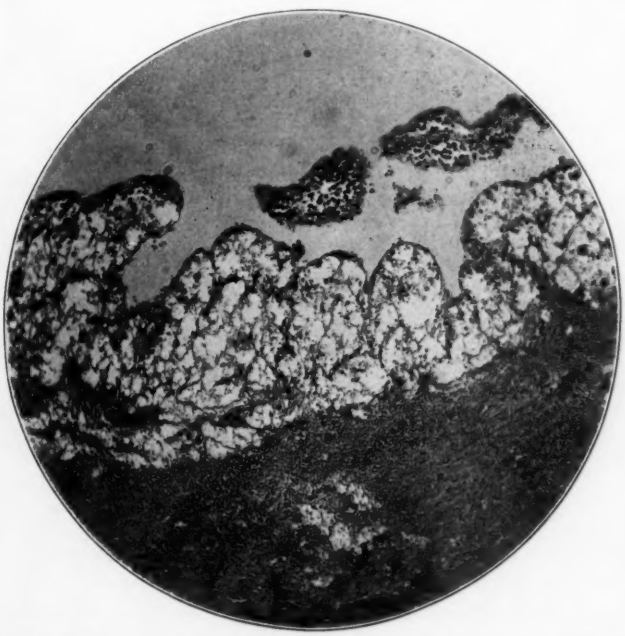

Fig. 7.—The wall of the gallbladder; the spongy network has probably come about through a fusion of the xanthoma cells.

there were much bile pigment and numerous polymorphonuclears in the latter. The parenchymal cells were small; the Kupffer cells were broadened by bile pigment and indefinitely outlined vacuoles. The picture was not suggestive of cramming of cholesterol. In frozen sections stained by sudan III the parenchymal cells were crowded with fine pigment granules, and at times with other granules which stained yellowish, as with a poor sudan III stain. It is surmised that these represented combinations of protein and fatty substances. In the Kupffer cells, however, deep red-staining globules (neutral fat) were seen in abundance. No crystals were found until a few widely distributed, doubly refracting ones were brought out under the polarizing microscope. Such crystals appeared always in the interstitial substance.

The wall of the gallbladder was only slightly thickened; in paraffin sections it measured 3 mm. in thickness. The mucous membrane was not recognizable; the lining consisted of a delicate membrane, evidently the basement membrane of the mucosa. The fibrous tissue immediately underlying the latter was coarsely reticular; apparently the tissue interstices had been tremendously overdistended, probably by lipoids. The resultant spaces were much larger than xanthoma cells and most irregular in form; they intercommunicated and contained moderate quantities of coarse pink granules. Moderate numbers of lymphoid and plasma cells (polymorphonuclears were absent) were located on the reticulum, whereas larger numbers occurred from place to place immediately under the basement membrane.

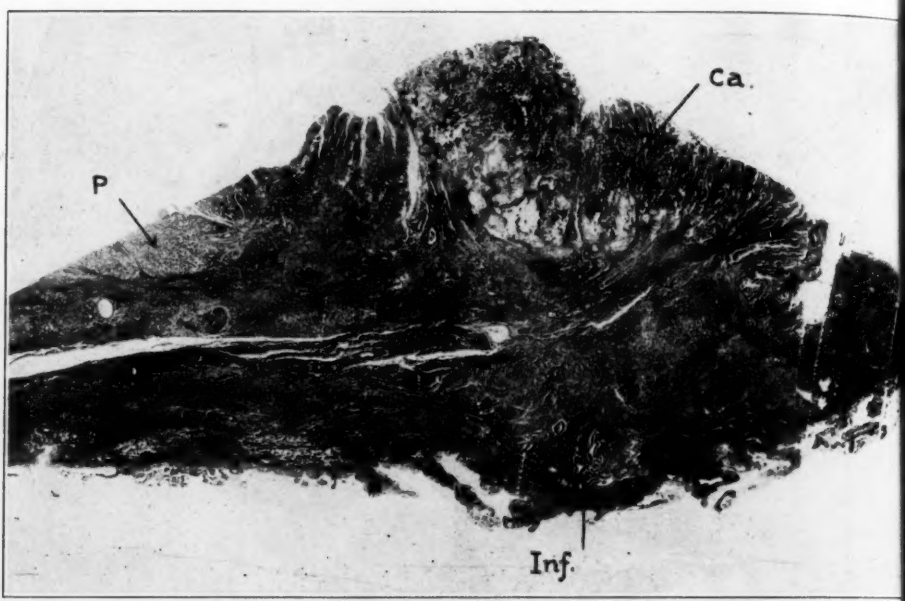

Fig. 8.—Adenocarcinoma of a duodenal papilla. Mucosa of the common bile duct is shown below; that of the duodenum, at the top. The pancreas is indicated by *P;* the cancer, by *Ca.;* parts infiltrated by cancer tissue, by *Inf.*

The capillaries in this region were highly congested. The same order of changes occurred focally from place to place in other locations, even in deeper parts of the muscularis, but far less intensely. Thus, the spaces occurred individually or as loosely connected, comparatively widely separated groups of spaces; that is, they were unlike xanthoma cells. The general effect given was that of a thin plaque of lipoidal infiltration located immediately under the mucous membrane, with scantier extensions into the muscularis. The glands appeared to be normal in number, but their lining cells were moderately hyperplastic and had large nuclei rich in chromatin. It did not appear that the acini had proliferated. The muscular tissue no longer appeared as such; it was represented by pink granular compara-

tively anuclear material disposed in strands between hyperplastic fibrous tissue bundles.

The mucosa of the common bile duct was recognizable on one side of the section by its plications; practically all of the epithelial covering had disappeared, as in the case of the gallbladder, leaving only the basement membrane as the surface covering (autolysis?). In general, the changes here were the same as those described for the gallbladder, including the lipoidally distended spaces, glands and infiltrate of round cells. The glands, however, were definitely hyperplastic and took on adenomatous configurations. They were so close to the focus of carcinoma which appeared on the intestinal side of the section that they were intermixed with plugs

Fig. 9.—Infiltration of muscular tunics by adenocarcinoma at the duodenal papilla.

of cancer cells which had obviously extended from it by direct metastasis. We do not believe that these glands were participating in the malignant phases of the situation. Indeed, at one place cancer cells were located immediately under the basement membrane.

The opposite side of the section permitted the recognition of intestinal mucosa. Irregular columns of disorderly hyperplastic cells extended perpendicularly from the surface with intervening partitions of involuntary muscle. The cells were in part simple and columnar, but in the deepest position exhibited metaplasia into rounded, polygonal or seal-ring forms. Not infrequently they occurred in strips or even as atypical tubules. The rounded and polygonal forms were found infil-

trating the deepest parts of the muscularis and extending even as far as the mucosa of the bile duct. Even in these advanced positions the conformation of some of the cell groups was acinar. Cytologically, the characteristics common to cancer cells were satisfied, such as the large size of the cell cytoplasm and the nucleus, the abundance of chromatin and the mitotic figures. Xanthomatous changes could not be recognized with certainty in any of the cancer cells. Portions of autolytic pancreas were included in this section; the most peripheral portion of the cancer infiltrated it, but it was clear that the pancreas itself was not participating in the malignant hyperplasia.

Fig. 10.—Xanthoma cells in the capsule of the spleen.

Moderate xanthomatosis of the muscle cells in the external tunica muscularis was the only explanation of the yellow streaks reported in the intestines at operation and necropsy.

The capsule of the spleen was of normal thickness; in several places it exhibited reticulated foci suggestive of gigantic, fused xanthoma cells. The outlines of the latter could not be made out, but the granular substance in the spaces contained small pyknotic nuclei which in a way resembled arterial atheroma. The reticular parts of the stroma were markedly thickened, but almost bare of lymphoid cells. There was no hyperplasia of the endothelium. Isolated xanthoma cells were identified in the pulp, but only after careful search. The splenic nodules were small but rich in lymphoid cells. The erythrocytes in the sinusoids appeared autolytic; blood pigment was normal in quantity.

In the paraffin sections of the adrenal glands the only abnormality consisted in the extreme scarcity of lipoidal globules in the pars fasciculatis; cytoplasms were coarsely granular in all parts of the cortex. In the frozen sections, all cells except those of the pars glomerulosa contained large numbers of small deep red-staining globules. In many areas, however, masses of large globules also occurred, but there were no crystals. The observations as to doubly refractile crystals were the same as those in the liver; i. e., there were only widely scattered, isolated crystals, even among the masses of deep red-staining neutral fat globules.

The paraffin sections of the kidney were not particularly informative; the positions occupied by the crystals in the pyramids could indicate edema morpho-

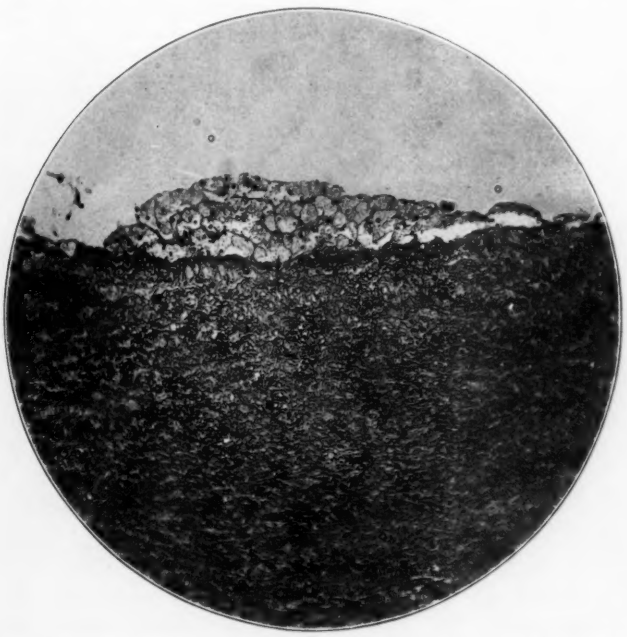

Fig. 11.—Intimal xanthomatosis, formation of xanthoma cells in the hyperplastic endothelium of the aorta. The pulmonary artery and the mural endocardium also exhibited this type of change.

logically as readily as they could lipoid content. The cytoplasm of the parenchymal cells appeared normal; cramming by cholesterol was not indicated morphologically. In addition to the abundance of bile pigment, which was to be expected, there were a few rather large masses of short, needle-shaped crystals in the frozen sections which had a greenish cast and which lay in the interstitial substance and not in the lumens of the tubules, as had been expected from gross observation. The crystals were doubtless the basis of the yellow striae that were commented on previously. With sudan III the crystals stained deeply red, whereas the bile pigment took an indifferent yellowish red color, something like that given by poor staining. Under

the polarizing microscope, only small numbers of the needle-shaped crystals were doubly refractive.

Short stretches of xanthoma cells lay on the intima (infiltrated endothelium) of the aorta with features readily distinguishable from those of atheroma; i. e., they had sharp outlines, did not fuse and had a distinctive piled-up appearance on the lining. In addition, poorly outlined clusters (foam cells) were discoverable in the media; these could not be distinguished from the foamy cells of atheroma. In frozen sections, great numbers of small deep red-staining crystal-like rods were found scattered throughout the intima both singly and in masses. In addition there were other rods of the same size and shape, which did not stain red. Very few of the crystals were anisotropic; as in the case of the liver, spleen and other organs, it was possible to identify them only at wide intervals. Although most of them lay in the intima, a few could be found also in the media.

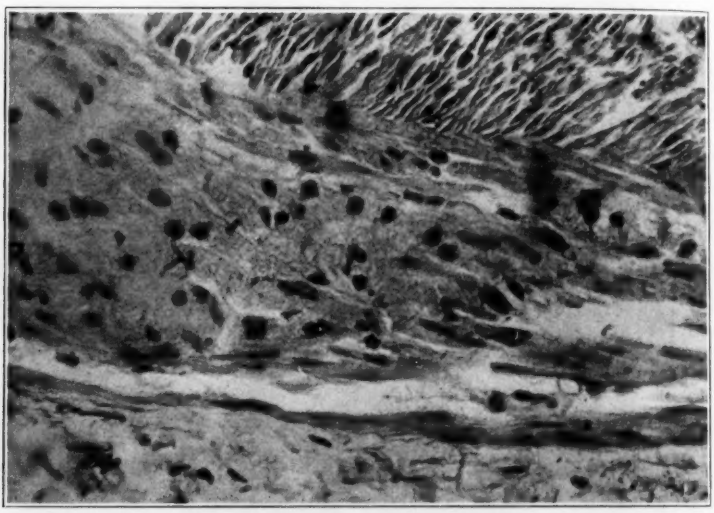

Fig. 12.—Beginning of foaminess in the cytoplasm of the smooth muscle cells of the intestinal wall. This focus is selected to demonstrate that it is the muscle cell and not the fibrous tissue that is concerned. Areolar subperitoneal tissue is visible at the bottom of the photograph.

Extreme grades of endarteritis nodosa were observed in most of the arteries examined, but there was no atheroma.

Paraffin sections of the skin reproduced the conventional picture of xanthoma tuberosum. The classic foam cells were distributed in groups or masses at all levels of the corium, but they still had a predilection for the upper strata, occurring even in contact with the basement membrane of the epiderm. They showed a tendency to be concentrated in certain more or less perpendicular tracts alined with the peripheries of hair follicles. This arrangement could be referred to concentration of the xanthoma cells in the larger lymphatic spaces which are known to surround such structures as hair follicles and blood vessels. A few of the xanthoma cells were multinucleated or so-called giant xanthoma cells. Cholesterol clefts were not seen.

As to the kinds of lipid in the skin of this patient, as revealed in a frozen section, by all odds the predominant one was neutral fat, which stained intensely red with sudan III. With the polarizing microscope it was possible to make out that there were also goodly quantities of doubly refracting lipoids in a more or less crystalline form. There were much larger masses of the latter in the skin than in the other organs which we have described and which were examined by this technic. We estimate that fully 50 per cent of the fatty substance in the skin consisted of doubly refractile substance (cholesterol?), and that the remaining 50 per cent was not doubly refractive (neutral fats and fatty acids).

Spindle cells were uniformly swollen throughout the section and loaded with large, red globules of neutral fat. Incidentally, the epiderm participated in the fatty change; as has been described by other authors, red globules were abundantly present in the basal cells. Furthermore, fat globules such as Pautrier [4] pictured, which he referred to as part of a purposeful transfer of particulate matter from the corium into the epiderm, were observable in spindle cells immediately below the basement membrane.

The mucosa of the urinary bladder was autolytic. The rest of the wall appeared normal.

Xanthomatous changes were not recognized in the pancreas. The only abnormality consisted in a moderate interlobular fibrosis.

Histologic Summary: First and foremost, a neoplasm was established as the cause of the biliary obstruction; it was primary in the mucosa of the bile duct. The gross diagnosis of biliary cirrhosis (not Hanot's) was confirmed.

All doubt was removed as to the nature of the yellow deposits in the splenic and hepatic capsules and on the mucosa of the gallbladder and the aortic lining; they were xanthomas and not simple atheromas or fatty degenerations.

Carcinomatous metastasis was not disclosed in any organ, nor were xanthoma cells observed extensively within the parenchymatous cells of an organ; there were only isolated xanthoma cells in the spleen and liver, which are the commoner depots for storage of cholesterol. That is, there was no evidence of surplus cholesterol, morphologically, except in the skin.

As to the particular kinds of fat indicated, in none of the viscera examined was it possible to find more than a few widely scattered short needles, which were anisotropic and which could be interpreted as cholesterol. There were great numbers of needle-shaped crystals of the same form as these, but they stained a deep red and were not doubly refractive. The inference is that the fatty substances in our case, at least by the time they reached the microscope, were in the form of neutral fat rather than cholesterol.

It should be added that the same changes were observed in frozen sections in two different lots of material. The first lot had been kept frozen for six days. The second lot had been promptly fixed in formaldehyde at necropsy, although the organs had been preserved for two days before sectioning. It is necessary to record such conditions in view of the known propensities for the fatty substances in xanthoma to undergo morphologic changes when preserved for some time in formaldehyde.

In view of the indefiniteness of xanthoma cells which so often obtains because of their vague boundaries, the situation in the wall of the gallbladder merits atten-

4. Pautrier, L. M.: Dermo-Epidermic Interchanges as Controlled by Study of Melanic Pigment, Esters of Cholesterol (Xanthoma) and Hemosiderin (Schamberg's Disease), Arch. Dermat. & Syph. **17**:1 (Jan.) 1928.

tion. Thus, the lipoid substances in the submucosal plaques lay free in tissue spaces, not in xanthoma cells. It was, in effect, a lipid edema, such as Bross[5] also noted.

PATHOGENESIS

Beginning with the hepatic disease, whether syphilis or carcinoma was the primary exciting factor, there resulted a high grade of hepatic damage, admittedly an outstanding cause of hypercholesteremia and consequent hyperlipoidosis. Thereafter, the genesis of the cutaneous lesions becomes understandable; in the presence of actively growing and actively dividing fibrous tissue cells, the excess fat entered the cell and was retained there, with the result that xanthoma cells were produced. We are unable to state what the incentive was to young fibrous hyperplasia in our patient, but the multiple abscesses were consistent developments on the skin and were perhaps secondary to the infection of the biliary tract. Evidently the old scars on this patient, such as the normal one at the umbilicus, that at the site of antismallpox vaccination and the syphilitic scars of the scalp and arms, were not in the appropriate biologic phase to accept and retain the substances.

Cause of the Hepatic Disease.—In our case, the conclusion as to which was the primary lesion in the disease complex—cancer or syphilis—is contingent entirely on the age of the lesion at the duodenal papilla. From the clinical history it appears that the disease began nineteen months before death supervened. The carcinoma was exceedingly small; it could not be delineated grossly, but was not more than from 8 to 10 mm. in diameter, as judged in histologic sections. It seems impossible to conclude finally that such a small carcinoma could be nineteen months old or, on the other hand, that it was of only recent development; one can only speculate. The features were not quite those of adenoma malignum, which is a form of carcinoma conceded to be very slow in growth. The carcinoma was definitely infiltrative. However, the absence of metastases in regional lymph nodes speaks for the comparative benignancy of this particular cancer. Adenomatous hyperplasias with minute polypoid formations frequently occur at the biliary outlet (Dardinski[6]), and may well have preceded the adenocarcinoma in our case.

On the other hand, it is possible to construct another hypothesis, such as that of an initial syphilitic hepatitis masked by the subsequently developing biliary obstruction; the mildness of the fibrosis of the liver could be invoked in support of this idea. This would imply that the hepatic damage antedated a biliary obstruction, but to us this line of thought

5. Bross, K.: Generalized Xanthomatosis, Virchows Arch. f. path. Anat. **227**:145, 1920.

6. Dardinski, V. J.: Inflammatory Adenomatoid Hyperplasia of the Major Duodenal Papilla in Man, Am. J. Path. **7**:519 (Sept.) 1931.

would lead to such interminable speculation as to the relative susceptibility of the liver and the wall of the gallbladder to irritants and as to various other involved considerations that this hypothesis cannot be fertile of results.

As to syphilis in the case, the serologic reports were conflicting; the Wassermann reaction of the blood was positive at the first examination and negative at the second. Much more important were the scars of the scalp and arms—favorite sites for syphilis. On the other hand, the aorta did not show the syphilitic type of arteritis at necropsy. We feel, however, that in this patient the balance of evidence decidedly favors syphilis, the cutaneous lesions turning the scales.

Our first impulse was to favor the hypothesis that there was an initial syphilitic cirrhosis accompanied by hypercholesteremia, and that the carcinoma finally became intercurrent. The obstruction thereupon added a biliary type of cirrhosis which masked the antecedent syphilitic cirrhosis. We were influenced somewhat toward this opinion because we had recently witnessed at necropsy a carcinoma of the stomach which was associated with a regressed xanthoma of the pons and xanthoma tuberosum of the skin.[1] It seemed more than a coincidence that two malignant tumors should be encountered in two consecutive cases of generalized xanthomatosis under the observation of the same physicians, particularly since necropsies in cases of generalized xanthomatosis are exceptionally rare.

At this point, the case of Kreibich [7] applies. Syphilis was likewise present in his patient, but at such an early stage (nine months) that cirrhosis at least could not have been a factor, although there was still a remote possibility that the arsenical therapy which the patient had received had played a part and caused hepatic damage. The welcome contribution to the immediate problem is Kreibich's citation of gastric crises as the occasion for a zoster, as in our patient; at least, similar neurologic considerations are involved. This item probably carries more weight than any other chronological evidence in our case, i. e., as to the duration of the lesion of the duodenal papilla. If one may assume that a lesion of the duodenal papilla inaugurated the zoster, it would establish itself rather than syphilis and hepatic damage as the initial factor in the entire disease complex, because it will be recalled that the zoster made its appearance only four months after the initial pruritus and three months after the onset of jaundice.

All things considered, we feel that an adenomatous polyp at the duodenal papilla was the beginning of the entire disease complex, and that the cancer developed secondarily on the polyp at a comparatively late date.

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7. Kreibich, C.: Zosteriform Xanthoma, Arch. f. Dermat. u. Syph. **152**:365 (Dec. 3) 1926.

INTERNAL XANTHOMATOSIS IN GENERAL

It is seldom that xanthomatous infiltrations have been demonstrated in internal organs in xanthoma tuberosum, largely because necropsies have been so rarely performed. The table which follows contains all the references we could find. Even in Pinkus and Pick's [8] case, although a necropsy and exhaustive studies were made, little was added to the knowledge of the internal distribution of xanthoma. In our case, the presence of the deposits in the capsules of the liver and the spleen, in the aortic intima and in the walls of the intestines connoted an association with endothelium (serous surfaces) which was consistent with the habits of xanthomatous infiltrations in general and thus explanatory of this distribution. Endothelium (compare the Kupffer cells in this case) is notoriously liable, together with fibrous tissue, to xanthomatous infiltrations. Only a few cases of xanthomatosis of the vascular endothelium appear to have been described in the literature. Low [9] stated briefly that there were (clinically presumptive) xanthomatous lesions on the heart valve. Similarly, the reports of Lehzen and Knauss [10] and of Pavy and Fagge,[11] although they described extensive yellow plaques grossly in arteries or on the mural endocardium (Balzer [12]), were not satisfying histologically; it was not clear whether the changes were xanthomatous or simply atheromatous. The situation will be illustrated at the end of the next paragraph; figure 11 illustrates clearly the difference between intimal xanthomatosis and ordinary atheroma. Although they occurred in a neoplasm, the changes which Petri [13] described in the walls of the blood vessels of a hemangioma fully qualify as xanthomatous.

In point of extensiveness of xanthomatous changes in the internal organs, our case was excelled by that of Bross; [5] cutaneous lesions, however, were confined to a faint, diffuse yellowing of the scrotum. As in our patient, there were yellow fleckings on the capsules of the spleen and liver and on the intima of the aorta and pulmonary arteries. The following additional lesions were described: multiple xanthomas of the kidneys, with a xanthomatous infarct of the left kidney; small xanthomatous foci in the prostate and the duodenal mucosa; lymphangiectatic

8. Pinkus, F., and Pick, L.: Xanthoma and Foam Cell Tumors, with Report of a Case of Generalized Xanthoma Tuberosum, Dermat. Ztschr. **15**:706, 1908.

9. Low, R. C.: Xanthoma Tuberosum Multiplex, with Lesions in Heart and Tendon Sheaths, Brit. J. Dermat. **22**:109 (April) 1910.

10. Lehzen, G., and Knauss, K.: Ueber Xanthoma multiplex planum, tuberosum, mollusciforme, Virchows Arch. f. path. Anat. **116**:85, 1889.

11. Fagge, C. H.: General Xanthelasma or Vitiligoidea, Tr. Path. Soc. London **24**:242, 1873.

12. Balzer, F.: Researches on the Anatomical Characters of Xanthelasma, Arch. de physiol. norm. et path. **4**:65, 1884.

13. Petri, E.: Xanthomatous Tissue Changes; Haemangioma Xanthomatosum, Zentralbl. f. allg. Path. u. path. Anat. **34**:1, 1923.

xanthomatosis of the appendix, the mesenteric and the retroperitoneal lymph nodes and of the bone marrow of the femur. The studies were conducted under Lubarsch's direction, and the xanthomatous nature of the lesions was established histologically. Bross emphasized that the xanthomatous processes involved interstitial substance exclusively and not the parenchyma. He commented properly that there had been numerous xanthomatous fleckings described previously as occurring on the capsules of organs, but without microscopic confirmation, and that his own observations would tend to demonstrate that the previous authors were correct in regarding the fleckings as truly xanthomatous. However, the yellow lesions on blood vessels are still to be considered questionably xanthomatous, as the lesions in his patient proved, under the microscope, to be at times xanthomatous and at other times simply atheromatous.

In Christian's disease the xanthomatous infiltrations are more widespread, in general, than in any other expression of xanthoma; flat bones, lungs, liver, spleen and brain are involved. This disease affects children almost exclusively, and has such a high mortality that numerous necropsy studies have been made possible. In these cases the blood cholesterol value runs exceedingly high, as much as 397 mg. per hundred cubic centimeters and more. Rowland [13a] entertained the belief that the disease is a dyslipoidosis essential to the reticulo-endothelial system. In the case which Weidman and Freeman [14] described as one of xanthoma tuberosum, and which can be admitted as one of Christian's disease, it was felt that the basic lesion was granulomatous and that xanthomatous infiltration was superadded. It is conceivable that the widespread visceral involvement in Christian's disease is explainable by the youth of the tissues concerned, i. e., the tissues of young persons being comparable to the tissues of a young scar, and the tissues of old persons to those of old scars.

Although necropsy was performed in one of Futcher's [15] cases, xanthomatous change was reported only in the bile ducts; as in our case, both the intrahepatic and the extrahepatic ducts were involved.

Between the skin and the internal tissues there appears to be no correspondence in the extent of xanthomatous involvement. For example, in Bross' case of most extensive internal xanthomatosis only a mild, diffuse yellowing externally, confined to the scrotum, was noted. In Christian's disease, with its extensive osseous involvement, the skin has

13a. Rowland, R. S.: Christian's Syndrome and Lipoid Cell Hyperplasia of the Reticulo-Endothelial System, Ann. Int. Med. **2**:1277 (June) 1929.

14. Weidman, F. D., and Freeman, W.: Xanthoma Tuberosum, Arch. Dermat. & Syph. **9**:149 (Feb.) 1924.

15. Futcher, T.: Xanthelasma and Chronic Jaundice, Am. J. M. Sc. **130**:939, 1905.

been found involved only once (Weidman and Freeman [14]). On the other hand, Pinkus and Pick [8] described extensive cutaneous xanthoma and an insignificant internal one. The following table is illustrative.

XANTHOMATOSIS IN MALIGNANT TUMOR CELLS

Infiltration of sarcoma cells by lipoidal substances, with the production of xanthosarcomas, is well known.[16] Analogous developments in carcinoma cells appear comparatively seldom; a catalog of such cases will appear elsewhere.[1]

Comparison of Cutaneous and Internal Xanthomatosis *

	Skin and Mucosae	Internal Lesions
Futcher [15]	Eyelids, palms, elbows, etc.	None mentioned
Pavy and Fagge [11]	Eyelids, hands, abdomen	Larynx, arteries, splenic capsule
Moxon: Tr. Path. Soc. London **24**: 129, 1873	Eyelids, hands, scrotum, etc.	Larynx, splenic capsule
Murchison: Tr. Path. Soc. London **20**: 187, 1869	Eyelids only	Spleen and kidney
Pye-Smith: Guy's Hosp. Rep. **22**: 97, 1877	Eyelids only	Cancer of duodenal papilla
Pinkus and Pick [8]	Face, trunk	None recorded
Balzer [12]	Trunk, neck, etc.	Mural endocardium
Bross [5]	Scrotum	Vascular intima, capsules of spleen and liver, appendix, tonsil, lymph nodes, kidneys, marrow
Various authors (cited by Sosman: J. A. M. A. **98**: 110 [Jan. 9] 1932)	None mentioned, except in tooth sockets	Bones, brain; other organs irregularly involved
Weidman and Freeman [14] (case 1)	Eyelids, elbows, buttocks, etc.	None
(case 2)	Eyelids, elbows, buttocks, etc.	Lungs, spleen, brain, etc.
Weidman and Boston (this case)	Elbows, knees, zoster scar, etc.	Intima of vessels, capsule of spleen and liver
Weidman and Schaffer [1]	Eyelids, elbows, arms, scrotum, etc.	Larynx, pons

* Although Gaucher's disease may not qualify as xanthoma, it should not be forgotten, with its involvement of the spleen and bone marrow (Pick: Veröffent. a. d. Kriegs.-u. Konst. Path. **4**: 3, 1927).

White [17] has emphasized the regularity with which large quantities of cholesterol were demonstrable in carcinoma; admittedly, however, the fat, if not confined to intercellular positions (which seems inconceivable), is in a different physicochemical state within the cytoplasm of ordinary carcinoma cells than it is in xanthoma cells.

Cholesterol and Cell Growth.—In our patient the combination of a continued and excessively high hypocholesteremia and the development of carcinoma at a relatively late stage of the hypercholesteremia must

16. Weidman, F. D.: Xanthosarcoma of the Cheek Succeeding Xanthosarcoma of the Forearm: Multiple Tumors Versus Metastasis, Arch. Surg. **34**:792 (May) 1937.

17. White, C. P.: On the Occurrence of Crystals in Tumours, J. Path. & Bact. **13**:3, 1909.

recall the continuous undercurrent of thought in many quarters as to the rôle of cholesterol in furthering the growth of cancer. In the experiments of Sweet, Corson-White and Saxon [18] on rats, metastases were increased tremendously when cholesterol was sprinkled on the inoculated tumor tissue. Luden [19] emphasized years ago how determinations of blood cholesterol should be of special value in the study of malignant growth because cholesterol promotes the multiplication of cells. Roffo [20] found three times more cholesterol in the tumor tissue than in the rest of the animal. Most recently Morelli and Focosi [21] emphasized the rôle of lipid metabolism: "The lipids of the lymphatic apparatus and of the reticulo-histiocytic system are of greatest significance for the formation of neoplasms." In short, this opinion concerning cholesterol has been asserted by such scattered and independent investigators that we cannot escape at least consideration of the rôle that lipids played in promoting the cancer in our patient. It is unnecessary to add that cholesterol cannot be the sole factor, any more than it is the sole factor in the determination of xanthomatous lesions. Nevertheless, the occurrence of cancer in this patient and of the cancers in the stomach [1] in two successive cases of xanthoma under the observation of the same physician and studied at necropsy is difficult to dismiss as a mere coincidence. This is particularly the case since the gastric carcinoma with metastases cited [1] was such an outstanding example, and since the xanthomatosis, connoting a general lipoid disturbance, had been present for more than ten years.

Xanthomatosis and Tumors in General.—In our patient the tumor was not xanthomatous. It is rare under any circumstances for epithelial cells to become outstandingly xanthomatous. Even in Pick's [22] extensive case of osseous Gaucher's disease, which involved a widespread hyperlipoidosis, the cancer of the bile duct was not described as xanthomatous. Tumors of the connective tissue, however, are liable to the change, particularly fibrosarcomas of the tendon sheaths. Since the tumor in our patient does not bear on this subject, reference is made

18. Sweet, J. E.; Corson-White, E. P., and Saxon, G. J.: Relation of Diets and of Castration to the Transmissible Tumors of Rats and Mice, J. Biol. Chem. **15**:181 (July) 1913.

19. Luden, G.: Cancer and Chemistry, Woman's M. J. **30**:1 (Jan.) 1923; Blood Cholesterol: Its Importance and the Value of Its Determination in Cancer Research, Canad. M. A. J. **12**:147 (March) 1922.

20. Roffo, A. H.: Cholesterol Ratio in Tumors, Prensa méd. argent. **11**:1060 (April 20) 1925.

21. Morelli, E., and Focosi, M.: Changes in Lipoid Metabolism Following Treatment with Cancer-Forming Substances, Ztschr. f. Krebsforsch. **34**:473 (Oct. 17) 1931.

22. Pick, L.: The Skeletal Form of Gaucher's Disease, Veröffentl. a. d. Kriegs- u. Konstitutionspath. **4**:3, 1927.

here only to other conditions (xanthosarcoma [16] and cancer of the stomach [1]) mentioned in the literature on xanthomatous tumors in general.

Suppurative Features.—Mention has already been made that a number of the xanthomatous lesions became suppurative, and that a small abscess developed in the lobe of the ear, apparently independent of a xanthomatous nodule. It was likewise stated that in the histologic sections of a xanthomatous nodule there was a perifollicular, polymorphonuclear infiltrate. This phenomenon, i.e., the complicating suppuration, is rare if not unique for xanthomatous nodules. Under these circumstances, the presence of a focus of extreme polymorphonuclear infiltration adjacent to the biliary neoplasm, together with the obvious stasis in the biliary tract, appears to be of importance. That is, it is surmised that the biliary lesion represented a focal infection from which a state of subinfection (in the sense of Adami) was induced, with localization thereafter in an abnormal focus such as a xanthomatous nodule.

In the last-named connection, a second interpretation must also be recorded, namely, that the cutaneous xanthomas began as microscopic abscesses—cutaneous metastases from the focal infection in the biliary tract. Under these circumstances, fibroblasts developed, which in the presence of a hypercholesteremia took on the character of xanthoma cells. While this explains the cytologic phases in the situation, it does not explain the distribution of the lesions, i.e., the predilection for the elbows and the knees. The latter distribution, however, was still not an exclusive one; other nodules were scattered rather widely elsewhere. The success of one of us (F. D. W.[23]) in one of his experiments with pneumotoxin on hypercholesteremic dogs may bespeak a toxic factor as one of several conditions which predispose cells to lipoid infiltration. We lean toward this second interpretation in our case; we give emphasis to the suppurative features because it is such exceptional incidents which have value in our search for the additional x, y and z factors which determine the formation of xanthoma cells and which are commonly and loosely referred to collectively as predisposition.

SCAR (AND ZOSTERIFORM) XANTHOMA

Considering scars in their broadest, general pathologic, i.e., regenerative, sense, there is a fairly long list of cases cited in the literature in which scars became xanthomatous. The more unequivocal examples, such as those following surgical operations and trauma, are rarer.

In Kreibich's [7] patient a zoster developed which, from its description, almost duplicated that in our case. Thus, jaundice developed in a syphi-

23. Weidman, F. D.: Studies in Hypercholesterolemia: III. Approach to the Pathogenesis of the Xanthomas, Arch. Dermat. & Syph. **15**:659 (June) 1927.

litic man who had a large, hard liver and in whom the spleen was palpable. Eventually, as in our case, the Wassermann reaction of the blood became negative. The blood cholesterol measured 750 mg. per hundred cubic centimeters (normal value by his technic, 200 mg. per hundred cubic centimeters). Papular xanthomas developed in groups in a zosteriform band involving dermatomeres from the sixth to the ninth; the illustration depicts a lesion that is practically identical with ours. Xanthomatous lesions were also present on both olecranons and knees, and the author emphasized the follicular character of many of the nodules. (The interpretation he placed on the latter was different from ours; it will be recalled that we believed that those in our patient were referable to minute traumatisms inflicted during shaving. Kreibich thought that the lesions were due to toxic nervous impulses.) Although he cited the rôle of gastric crises (ulcer, cancer, vomiting and tabes) in the development of zoster, it appears that a final opinion was not arrived at as to the exact nature of the gastric lesions in his patient.

The effect of Kreibich's experience was that we attributed the development of the zoster lesion in our patient to an analogous origin in the gastro-hepatic region, most reasonably the polyp at the ampulla of Vater. If this is admissible, it would go far toward establishing the age of the carcinoma in our patient, about which we have been so much perplexed. Since the zoster lesion occurred at the fourth month of the disease, it will be reasonable to suppose that the polyp likewise was present at least that early.

Kreibich also expressed a number of new thoughts in respect to the etiology of xanthoma. The zosteriform lesions in his patient were not inflammatory. Hence he assumed that they were referable not to inflammation but to exalted tonus of the skin cells induced by exaggerated efferent impulses which in the final analysis emanated from the stomach; that is, the xanthoma lesions had a morbid-physiologic rather than a material basis in causation. He explained the follicular distribution on the same basis—that it was due to physiologic stress put on the hairs; that is, a lesser grade of stimulus than that of inflammation sufficed to initiate the xanthomatous processes. Kreibich cited the acne zosteriformis of Blaschko as analogous to his zosteriform xanthoma, which, it appears, is also due solely to nerve stimuli.

As Kreibich did not record the history of the development of the zosteriform lesions, it is probable that they were not observed by a dermatologist at the beginning. It is thus possible that the original lesions were red papules, i.e., abortive zoster as in our case, and that by the time they came under Kreibich's observation they were papular xanthomas. Again, the acneform arrangement of Blaschko's acne zosteriformis could, similarly, be explained as the consequence of zosteriform scars the contractions of which had widened the follicular orifices.

Hardaway [24] also mentioned a zosteriform arrangement as part of a xanthomatosis involving the mucosae, tendons and subcutaneous tissue. Only an abstract of his paper was published; hence one cannot compare his case with ours and analyze it in the modern light. Hepatic disease was present, however, and Hardaway remarked that the zosteriform xanthomas "might have resulted from an abortive attack of herpes zoster."

To return to scars proper, the most fully studied case we found was that of Urbach.[25] In the scar of a tuberculo-ulcerous syphilid he observed the development of fifteen xanthomatous nodules. A most comprehensive chemical study of the blood and other fluids was made, but no abnormalities were found; the blood cholesterol was well within the normal limits on two examinations. In short, the xanthomas developed in syphilitic scars in the absence of a hypercholesteremia or other demonstrable metabolic upsets. Urbach concluded that the source of the fat was in the local inflammatory-degenerative processes existing at the site of the syphilitic process (an age-long theory), and that in the presence of a lipoid surcharged serum in this situation the fibrous tissue cells absorbed the fat.

One of us (F. D. W.) presented for Gittings [26] at a meeting of a dermatologic society a child, aged 3 years, in whom there were highly developed xanthomatous lesions in a laparotomy scar and in the gums, in the latter site succeeding the extraction of teeth. The patient was presented both for this reason and because similar changes were absent in *old* scars, such as those at the umbilicus and at the site of an antismallpox vaccination. The blood cholesterol value for this patient was 1,067 mg. per hundred cubic centimeters. The case will be reported in full by Weidman and Stokes.[27]

Posner,[28] too, reported briefly and incidentally the development of a laparotomy scar richly studded with xanthomatous nodules in a woman, aged 37. The nodules were particularly conspicuous in the stitch holes.

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24. Hardaway, W. A.: Xanthoma Multiplex of Skin Mucosæ, J. Cutan. & Ven. Dis. **2**:353, 1884.

25. Urbach, E.: True Xanthoma or Xanthomatosis Degeneration of the Skin, Klin. Wchnschr. **2**:542, 1923.

26. Gittings, J. C.: Xanthoma Tuberosum with Jaundice, Arch. Dermat. & Syph. **17**:730 (May) 1928.

27. Weidman, F. D., and Stokes, J.: Extensive Xanthoma Tuberosum in Childhood Due to Infectious Cirrhosis of the Liver, Am. J. Dis. Child. **53**:1230 (May) 1937.

28. Posner, O.: Symptomatic Xanthoma in Chronic Icterus, Deutsche med. Wchnschr. **35**:96, 1909.

Although he did not see the patient, Schmidt [29] reported numerous xanthomas in a scar made by an excision; the case came to his notice when the blood was referred to him for examination. The blood cholesterol measured 194, 392 and 414 mg. per hundred cubic centimeters at different periods.

Ochs [30] presented a girl, aged 7 years, at a meeting of a dermatologic society. In addition to lesions on the fingers and elbows, there were a few on the buttocks at the site of former therapeutic antisyphilitic injections. The injections were made at the age of 9 months. In a personal communication, Ochs added that the Wassermann test of the blood was negative, and that the skull, elbows, wrist, feet and all bony structures were normal roentgenologically; i. e., that the condition was not Christian's disease. Blood cholesterol measured 800 mg. per hundred cubic centimeters; lecithin, 367.5 mg.; uric acid, 2.9 mg.; urea nitrogen, 10.8 mg.; sugar, 75 mg., and chlorides, 526 mg. Two of the physicians who commented on his presentation felt that the site of the nodules was not at the points of injection; nevertheless, Ochs' view was strengthened by the presence of additional xanthomatous lesions around the scar caused by vaccination, which is rather conclusive. This brought the condition unequivocally into the category of xanthoma developing from scars.

In the same category belong the xanthomas which Major [31] recorded as developing around mosquito bites on the forehead of a diabetic boy of 16. The blood cholesterol in this case was 400 mg.

Papular xanthoma developed in and around a scar following an operation for hernia on a child, aged 11 years (Artom [32]). A widespread erythrodermia developed subsequently; when it disappeared, numerous xanthomatous papules remained. Here again, youthful tissues were concerned.

From xanthoma occurring in scars, which may be regarded as such in the strictest sense, it is but a step to the development of xanthoma in reactive tissue incidental to inflammatory skin lesions.

Pinkus and Pick's [8] patient, who was xanthomatous after recovering from an intercurrent attack of erysipelas, exhibited a residual, diffusely xanthomatous skin at the site of the erysipelatous lesion. At necropsy, Hanot's cirrhosis, pneumonia, diffuse pulmonary tuberculosis, a tuberculous pericarditis and peritonitis, tuberculosis of the spleen, internal

29. Schmidt, E.: The Xanthoma Question, Arch. f. Dermat. u. Syph. **140**:408, 1922.

30. Ochs, B.: Xanthoma Tuberosum, Arch. Dermat. & Syph. **22**:922 (Nov.) 1930.

31. Major, R. H.: Xanthoma Diabeticorum, Bull. Johns Hopkins Hosp. **35**:27, 1927.

32. Artom, M.: Papular Xanthoma, Gior. ital. di dermat. e sif. **68**:1060, 1927.

pachymeningitis and cholelithiasis were revealed. No statement was made as to the cholesterol content of the blood.

A more tardy development of xanthomas was observed by Lehzen and Knauss [10] in two sisters, aged 9 and 11. The younger child had festers all over the body at 3, the xanthomas appearing at 4. The other sister had suffered a vesicular eruption preceding the xanthomas, but a useful dermatologic history could not be obtained.

Weidman's [23] observations on an experimentally cholesterolized dog in part paralleled the foregoing experience; a diffuse xanthomatous infiltration developed in an intercurrent cellulitis of the scrotum. It is curious that in spontaneous xanthomas of man the scrotum is also commonly affected.

Likewise, but not quite so clearly, a case of xanthoma with secondary keloids may belong in this series of cases of xanthoma developing in scars. Legendre, Joltrain and Levy-Franckel [33] called attention to xanthomas of the arms, forearm and hands; however, they contended that the associated keloids were secondary. They studied their patient exhaustively; the blood cholesterol measured 300 mg. per hundred cubic centimeters and the total fat from 4,121 mg. to 5,545 mg. The serum was milky at all times, regardless of the diet and the time of day. These investigators injected the lipoidal extract from the serum into the skin of rabbits, following which a nodule that seemed to be sclerosed developed. A photograph of the arm showed typical linear keloids, with xanthomatous nodules in the adjacent vicinity. One would be tempted, indeed, to conclude that the sequence of events in this case had been like that in Urbach's case—that the xanthomas were secondary—were it not that the studies were evidently carefully conducted. Thus, in observing the development of a keloid, the authors found that it began as a macule and changed first to a tuberous papule, then to a xanthomatous plaque and thereafter to fibrous and keloidal plaques. They emphasized that the keloids were secondary, not primary, lesions.

Pathogenesis of Xanthomatous Scars.—In an attempt to reproduce scars experimentally, one of us (F. D. W.[23]) induced them in ten hypercholesteremic volunteers by surgical removal of biopsy material from the elbow. All the subjects were elderly and affected with nephritis, arteriosclerosis or diabetes—diseases liable to complications by hypercholesteremia. Although the values for blood cholesterol ranged between 264 and 448 mg. per hundred cubic centimeters, xanthomatous lesions did not develop, nor were xanthoma cells found in the excised skin, even in the face of such a high concentration of blood cholesterol. It is generally agreed that hypercholesteremia alone cannot account for the development of xanthomas; the appropriate conditions in cellular metabolism

33. Legendre, R.; Joltrain, E., and Levy-Franckel, G.: Xanthoma General and Disseminated with Secondary Keloids, Bull. méd., Paris **26**:1043, 1912.

must accompany it, and it appears that these do not regularly obtain in simple uncomplicated regeneration such as occurs in clean surgical wounds. The development of xanthomatous changes resides as much in the cell as in the fluid in which the cell is reared.

Hermann and Nathan [34] had the same experience; in a boy with hundreds of xanthomatous nodules there was no development of xanthoma in a 2 year old scar. Likewise, in a sister of about the same age none developed in scars caused by biopsy. The brother did not exhibit hypercholesteremia, but the sister's blood yielded a cholesterol value ranging between 300 and 580 mg. per hundred cubic centimeters on five different occasions.

With this information, the way to an understanding of the mechanism of the development of xanthomas in scars is clearer. To begin with, Anitschkow [35] showed in the beginning of the knowledge of xanthomatous changes that fat could be demonstrated within granulation tissue cells of healing wounds in *normal* rabbits. However, if hypercholesteremic rabbits were employed, the fats in these cells were found to be lipoid; i. e., they contained cholesterol (presumably) rather than neutral fats. His classic experiment, employing seta (bits of cork dipped in turpentine), led to the development of xanthomatous cells; this, in principle, may be regarded as the development of xanthomatous changes in scars. One may surmise that *young* fibrous connective tissue cells are members of a group of cells which have an inherent propensity to take up fatty substances from the environment.

In the development of the xanthoma cell per se, the original source of the lipids, whether local or part of a general hyperlipidosis, is not pertinent. Stewart [36] compiled a long list of local lesions (local in the sense that the hypercholesterosis is not generalized as part of an associated hypercholesteremia), such as dermoid cysts and galactoceles, in which xanthoma cells will be found. That is, local conditions may account for an excess of lipids, such as obtain in connection with inflammatory and associated degenerative processes, under the influence of which the immersed, actively growing fibrous tissue cells become stored and swollen with lipids. This would explain the xanthomas in the syphilitic scars which Urbach [25] described, and with which there was no associated hypercholesteremia.

On the other hand, wherever there is general hyperlipidosis, local lymphatic saturation is guaranteed, and it is then necessary only to add

34. Hermann, F., and Nathan, E.: Genesis of Xanthomas, Arch. f. Dermat. u. Syph. **152**:575, 1926.

35. Anitschkow, N. H.: Experimental Investigation on the Deposition of Cholesterol in Subcutaneous Tissue, Arch. f. Dermat. u. Syph. **120**:627, 1914.

36. Stewart, M. J.: On the Cellular Reactions Induced by Local Deposits of Cholesterol in the Tissues, J. Path. & Bact. **19**:305, 1915.

appropriate local conditions in respect to fibrous and other cells to understand the development of a local xanthomatous focus. This was the situation in Gittings' case, in Pinkus and Pick's case of erysipelas, in the experimental dog studied by one of us (F. D. W.) and in our case of zoster. If one is to accept the opinion of Legendre, Joltrain and Levy-Franckel, namely, that the keloids succeeded xanthoma, one must conclude that the formation of a scar did not enter into the xanthomatous aspect of his case; i. e., that these scars were sequelae and were residual after the xanthomatous infiltrations had become absorbed.

For the sake of convenience in clinical expression, we propose herewith the designation "scar xanthoma" in cases in which scars are in any way concerned in xanthomatous processes. As already indicated, scar xanthomas may occur entirely apart from hypercholesteremia, or, being part of a general hypercholesteremia, may be of diagnostic value and point in the direction of a grave fault of metabolism which in turn may be referred to important anatomic disease. Attention is called to the ages (3, 7 and 11 years) at which some of the scar xanthomas developed.

Operative Intervention in Xanthomas.—This is generally directed at the biliary tract in view of the jaundice which usually attends, i. e., quite regardless of the associated xanthomatosis. Only a few cases have been reported.

The exploratory laparotomy performed on Weidman and Stokes' [27] patient was in the nature of removal of tissue for biopsy; hepatic tissue was obtained for histologic examination.

The lesion at the duodenal papilla in our patient was so indefinite that it was not identifiable as cancer at either operation or necropsy. In any event, the cardiac failure which overtook the patient prevented a just estimate of what the surgeon might achieve with a fair opportunity. Incidentally, although the patients were not operated on, one should remember that cancerous lesions at the duodenal papilla have been met in previously reported cases of xanthoma (Pye-Smith's [37] case at necropsy and Moxon's [38] case of a noncancerous stricture). As to the cutaneous involvement in these cases, only the eyelids were affected in the first, but the xanthomatous lesions were extensive in the second. Cancer of the bile duct was also associated in one of Pick's cases of skeletal Gaucher's disease, which is related at least to xanthoma, although there were no cutaneous lesions.

In three instances the patients survived operation. In Wijnhauson's [39] patient, traumatic pancreatitis was largely corrected; interest-

37. Pye-Smith, P.: Vitiligoidea or Xanthoma, Guy's Hosp. Rep. **22**:97, 1877.

38. Moxon, W.: Simple Stricture of the Hepatic Duct, Causing Chronic Jaundice and Xanthelasma, Tr. Path. Soc. London **24**:129, 1873.

39. Wijnhauson, O. J.: Xanthomatosis in Recurrent Pancreatitis, Berl. klin. Wchnschr. **58**:1268, 1921.

ingly, crops of xanthomas preceded the several abdominal crises which were incidental to the pancreatitis. One of Futcher's [15] patients, who had an extensively xanthomatous involvement dermatologically, was cured after the removal of gallstones. A second, with only xanthoma of the eyelid, was not improved. There was hypertrophic cirrhosis without gallstones. Posner's [28] experience was almost identical.

In the laryngeal cases of Finney [40] and of Pusey and Johnstone,[41] tracheotomy became necessary. It may be added that xanthomas also occurred on the gums and in the laparotomy scars in certain of the aforementioned cases in which operation had been resorted to.

SUMMARY AND CONCLUSIONS

In connection with an extreme hypercholesteremia (1,020 mg. per hundred cubic centimeters) in a patient with generalized xanthoma tuberosum, an acute xanthoma succeeded an intercurrent herpes zoster. At necropsy, severe biliary cirrhosis was found, which explained the hypercholesteremia. A polyp at the duodenal papilla was probably the primary factor in the disease complex. Since the polyp eventuated in adenocarcinoma, attention is recalled to the rôle of cholesterol in promoting cell division and possibly cancerous hyperplasia.

In addition to cutaneous xanthomatosis, the deposits also occurred internally. They appeared as plaques (in relationship with endothelium) on the splenic and hepatic capsules, in the intima of the great vessels of the neck and in the muscular tunic of the intestine. The tabulation given shows the range of cutaneous and visceral involvements in all of the reports of necropsy available.

The lipids of the xanthoma cells were preeminently neutral fats and not the cholesterol esters suggested by the hypercholesteremia and emphasized in the older literature.

Cutaneous xanthomatosis should prompt examination first, not alone of the cholesterol content of the blood but of the lipids in general. Thereafter search should be made in respect to all conceivable causes already established for hepatic disease.

Instances of scar xanthoma are collected and analyzed; actively growing fibrous tissue, whether in a local scar or in juvenile patients in general, appears to contribute factors leading to the development of

40. Finney, W. P.: Xanthoma Multiplex with Involvement of the Upper Part of the Respiratory Tract, Proc. Staff Meet., Mayo Clin. **6**:667 (Nov. 11) 1931. Finney, W. P.; Montgomery, H., and New, G. B.: Xanthoma Multiplex, J. A. M. A. **99**:1071 (Sept. 24) 1932.

41. Pusey, W. A., and Johnstone, O. P.: A Case of Xanthoma Diabeticorum and Lipoma Multiplex and a Case of Xanthoma Approaching the Diabetic Type with Diabetes Insipidus, J. Cutan. Dis. **26**:552, 1908.

xanthoma cells. The cells in old scars and in simple regeneration do not tend to become xanthomatous. The application of this observation to spontaneous xanthomas is pointed out; i. e., that a preceding dermatosis may in some cases be the incitant to the formation of xanthoma. To what extent this operates remains to be determined. Local cutaneous suppuration, present in our patient, may have been the incitant to xanthomatous formation by provoking the formation of young fibrous tissue.

Instances of surgical intervention in connection with xanthoma are collected and abstracted. Marked improvement succeeded in only one case.

NITROGEN AND SULFUR METABOLISM IN BRIGHT'S DISEASE

VIII. EFFECT OF INGESTION OF UREA ON NITROGEN EXCRETION AND SULFUR PARTITION IN NEPHROSIS, GLOMERULONEPHRITIS AND CIRRHOSIS OF LIVER

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Previous studies have called attention to the strongly positive nitrogen and sulfur balances in patients with the nephrosis syndrome [1] and to the tendency to negative balances in patients with chronic glomerulonephritis.[2] More recently retention of urea was noted in a patient with nephrosis,[3] confirming the earlier observations of Peters.[4] Later observations by Peters [5] were interpreted by him as indicating a similar retention of urea fed to normal subjects, though of lesser degree than was the case in patients with nephrosis. These conclusions were contested by Kocher and Torbert,[6] who, however, failed to repeat Peters' experimental conditions, as they studied subjects on protein-free diets whereas all the other experiments were done by feeding urea to subjects on an adequate mixed diet. It seemed desirable to see if further experiments could be devised to reconcile the contradictory findings, which may be summarized as follows: Peters reported the retention of huge amounts of crystalline urea fed by mouth to patients with so-called chronic nephrosis. In a recently published case we have confirmed these findings. On the other hand, Peters reported the retention of small amounts of urea fed to the normal human subject. His findings in the normal subject were explained by Kocher and Torbert by calling attention to the delayed excretion of the extra urea in Peters' experi-

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1. Grabfield, G. P.: J. Clin. Investigation **9**:311, 1930.
2. Grabfield, G. P.: J. Clin. Investigation **10**:309, 1931.
3. Grabfield, G. P.: Nitrogen and Sulphur Metabolism in Bright's Disease: IV. Retention of Urea in the Nephrosis Syndrome, Arch. Int. Med. **52**:632 (Oct.) 1933.
4. Peters, J. P., and Moore, D. D.: J. Clin. Investigation **6**:5, 1928.
5. Moore, D. D.; Lavietes, P. H.; Wakeman, A. M., and Peters, J. P.: J. Biol. Chem. **91**:373, 1931.
6. Kocher, R. A., and Torbert, H. C.: J. Biol. Chem. **95**:427, 1932.

ments, though their own experiments were done on fasting subjects. All the studies so far lack various elements of certainty, such as analyses of the food and of the stool in some, and the experimental conditions have varied. None has included an investigation of the excretion of sulfur, and none has taken account of the proteinuria. It seemed worth while, therefore, to repeat the experiments, supplying all the missing conditions so far as possible.

In order to make this comparison, we deviated from Peters' regimen, in that our doses of urea were less, but it was not deemed advisable to give as large doses to a patient with glomerulonephritis as can be easily taken by patients with nephrosis, for example. It therefore seemed desirable to give the same dose of urea (20 Gm. a day) throughout all the experiments. We carefully selected two patients whose conditions represented as nearly pure examples of the nephrosis syndrome and glomerulonephritis as was possible. As we have previously presented evidence suggesting that an extrarenal mechanism might explain the metabolic findings, it seemed desirable also to include a patient presenting a classic picture of alcoholic hepatic cirrhosis. As a further control, one of us was studied on the regimen to be outlined presently. The important differentiating laboratory findings in these cases are presented in table 1. Case histories and detailed results of the experiments are also included. The purpose of this regimen was to provide an adequately balanced diet which would have the minimum of chemical variation from day to day. It was evident that such a condition could be best obtained by feeding exactly the same foods in constant amounts every day of the experiment. Such a diet is monotonous, and only the perfect cooperation that we obtained from the patients and the dietitians enabled us to use these ideal experimental conditions. Careful investigation by the dietitians of the patients' likes and dislikes enabled them to provide a diet that the patients were able to eat for four weeks. Care was taken to provide the same cut of meat and similar portions of vegetables. The diet was calculated from standard diet tables. Duplicate diets were then prepared every day (in some experiments, twice a week) and were analyzed by periods (table 2). Care was taken to reduce loss of water in cooking to a minimum, and the duplicate diets were cooked simultaneously and in similar containers. The food was weighed before and after cooking to check the loss of water. Fluids were measured, and sufficient was given to make the daily total constant, including the amount of water in the food. No salt was used in cooking, and a weighed amount of sodium chloride was given each day. Collections of stool were made daily, the various periods being marked by carmine or charcoal. The total nitrogen and sulfur of the stool was determined from a sample of the mixed stool for the entire period. Collections of urine were made daily under toluene or preserved with thymol dissolved in chloroform. The bottle for urine was kept in an icebox by the bedside, and the patient voided directly into the bottle. Urinary analyses for creatinine, total nitrogen, urea nitrogen, amino-acid nitrogen and the complete sulfur partition were made daily, both for the urine as voided and for the filtrate after the protein had been precipitated by heat and 0.5 per cent acetic acid. The solution of urea was analyzed both for total nitrogen and for urea, and it contained by analysis 497 mg. against a theoretical 500 mg. in the samples analyzed. In the calculations we have used the theoretical nitrogen content.

Standard methods of analysis were used: the Folin[7] methods for creatinine, total nitrogen, urea and amino-acid nitrogen and the Fiske[8] methods for the sulfur partition. Feces and food were dried after acidifying with hydrochloric acid and then analyzed for nitrogen by the Kjeldahl method and for sulfur gravimetrically by oxidation with sodium peroxide and precipitation as barium sulfate. The results in the individual cases are given in detail in the accompanying

TABLE 1.—*Data for Three Patients*

	Nephrosis	Nephritis	Cirrhosis
Blood: urea nitrogen, mg. per 100 cc.	14	11-21	11
nonprotein nitrogen, mg. per 100 cc.	38	35	23
total protein, Gm. per 100 cc.	4	6.6	7
albumin, Gm. per 100 cc.	1.7	3.9	4.1
globulin, Gm. per 100 cc.	2.3	2.7	2.9
cholesterol, mg. per 100 cc.	615	275	..
calcium, mg. per 100 cc.	..	10.3	..
phosphate, mg. per 100 cc.	..	4	..
creatinine, mg. per 100 cc.	..	1.2	..
Phenolsulfonphthalein excretion, percentage	45	65	..
Urea clearance, percentage	88-82	80-87	..
Galactose, Gm. excreted in five hours	..	..	12
Bromsulphalein	..	..	Normal
Urinary albumin	Large trace	Very slight trace, slight trace	0
Urinary sediment	Double refractile lipoids	Casts, ++	0
Hemoglobin, percentage	80-100	100	55-90
Erythrocytes, million	4.1-5.5	5.4	2.7-4.5
Leukocytes, thousands	10-15	8-10	5.4-8.1

TABLE 2.—*Detailed Data on the Diet of Three Patients and One Normal Subject*

	Nephrosis		Nephritis		Cirrhosis		Normal	
Daily Intake	From Tables	By Analysis	From Tables	By Analysis	From Tables	By Analysis	From Tables	By Analysis
Calories	2,569	.....	2,472	.....	2,446	.....	2,644	.....
Carbohydrate, Gm.	314	.....	201	.....	209	.....	249	.....
Fat, Gm.	100	.....	148	.....	146	.....	147	.....
Protein, Gm.	104	100.2	85	83.7	75	79.8	81	80.6
Sulfur, Gm.	1.20	1.22	1.07	1.02	1.13	1.12	1.21	1.19
Sodium, Gm.	1.25	.....	1.16	.....	1.25	.....	1.50	.....
Chlorine, Gm.	1.90	.....	1.78	.....	1.85	.....	2.24	.....
Sodium chloride as such, Gm.	2.00	.....	1.00	.....	4.00	.....	4.00	.....
Water of food, Gm.	1,665	1,653	1,541	1,643	1,551	1,646	1,697	1,674
Water as such, cc.	736	.....	1,000	.....	1,080	.....	1,200	.....
Total water intake, cc.	2,401	.....	2,541	.....	2,631	.....	2,897	.....

protocols, and summarizing tables from these results are included to facilitate discussion. In these tables the results are presented as of three periods in each case, the first being the control period, the second the period of administration of urea and the third the posturea period. The posturea period is divided into two

7. Folin, O.: Laboratory Manual of Biological Chemistry, ed. 5, New York, D. Appleton-Century Company, Inc., 1934.

8. Fiske, C. H.: J. Biol. Chem. **47**:59, 1921.

sections, the latter of which represents the return to normal and the first an intermediate period between the administration of urea and such a return. The numbers in these tables represent the average daily figure for the period.

CASE 20.—A white man aged 22 first entered the hospital on Sept. 21, 1933, complaining of swelling of the legs and pain in the back. He had been well until ten weeks before entry, when without previous illness or a history of medication or exposure to renal irritants, he first noticed swelling of the ankles and legs. At that time he stayed in bed under medical care, with relief of symptoms. On getting up he had an ache in the right iliac region, and the swelling reappeared. The cycle of edema when he arose and disappearance of the edema when he was in bed continued for ten weeks. He had felt listless and had had some mild headaches. Physical examination revealed tenderness on pressure in the right iliac region and edema of the ankles and apparently of the uvula. The urine showed a specific gravity of 1.025 and contained a large amount of albumin and many red blood cells and casts. The blood pressure was 134 systolic and 82 diastolic. The urea nitrogen content of the blood was 7 mg., and the nonprotein nitrogen content was 22 mg., per hundred cubic centimeters. Chemical analysis of the blood showed: total protein, 4.5 Gm.; albumin, 2.1 Gm.; globulin, 2.4 Gm. Excretion of phenolsulfonphthalein was 65 per cent. On August 24 the average urea clearance was 85 per cent. In September a chemical analysis of the blood showed: total protein, 4 Gm.; albumin, 1.7 Gm.; globulin, 2.3 Gm.; cholesterol, 615 mg., and nonprotein nitrogen, 38 mg., per hundred cubic centimeters. Throughout the patient's stay in the hospital there was mild leukocytosis but no anemia. The urine constantly showed a large amount of protein and a moderate number of casts. The patient was readmitted to the hospital for these experiments and showed findings that were essentially unchanged, except for a diminution in the excretion of phenosulfonphthalein to 45 per cent, which ultimately decreased to 20 per cent. He was discharged after the completion of these experiments, apparently in the same condition as on entry. He was readmitted a number of times and showed a steadily decreasing renal function. He died on Nov. 11, 1935. Autopsy showed contracted kidneys typical of chronic parenchymatous nephritis.

CASE 21.—A white man aged 23 was admitted to the hospital on Sept. 7, 1934, for the present study. His family history was of no importance. Five years before he had bilateral otitis media and two years before scarlet fever. He had nonspecific prostatitis six months before. In August 1933 he was admitted to the surgical service of the hospital for removal of a pilonidal cyst. At that time albuminuria was noted. From that time on he was followed in the medical outpatient department. On Jan. 9, 1934, examination of the blood showed: total protein, 7.2 Gm.; albumin, 4.1 Gm.; globulin, 3.1 Gm., and nonprotein nitrogen, 20 mg., per hundred cubic centimeters. The albuminuria had persisted. Shortly before he entered the hospital for the present study he was infected over the face and right hand with poison ivy, but the inflammation had almost disappeared. Physical examination revealed dilatation of the right pupil due to medication for iritis, for which he had been treated at the Massachusetts Eye and Ear Infirmary during the ten days before his admission for the present study; otherwise there was no remarkable finding. The blood pressure was 130 systolic and 80 diastolic. The other laboratory findings are given in table 1. He remained free from symptoms during his stay in the hospital.

CASE 22.—A white man aged 38 first entered the hospital on June 26, 1934, because of hematemesis three hours before. He had a syphilitic lesion in 1920, which had been treated with mercury and arsenic for two years. In 1919 and

TABLE 3.—*Data for Patient (Case 20) with Nephrosis*

		Urine as Voided										Protein-Free Urine							
Date, 1933	Body Weight, Kg.	Creatinine, Mg.	Total Nitrogen, Gm.	Urea and Ammonia Nitrogen, Gm.	Amino-Acid Nitrogen, Mg.	Total Sulfur, Mg.	Total Sulfate, Mg.	Inorganic Sulfate, Mg.	Ethereal Sulfate, Mg.	Neutral Sulfur, Mg.	Urine, Cc.	Total Nitrogen, Gm.	Urea Nitrogen, Gm.	Amino-Acid Nitrogen, Mg.	Total Sulfur, Mg.	Total Sulfate, Mg.	Inorganic Sulfate, Mg.	Ethereal Sulfate, Mg.	Neutral Sulfur, Mg.	Period
10/28-29	55.8	1,234	11.6	7.2	167	588	405	383	22	183	1,333	9.9	7.2	161	552	388	373	13	164	
10/29-30	56.0	1,504	11.8	7.4	201	592	467	373	94	125	1,475	8.5	7.4	197	543	425	354	71	118	
10/30-31	55.9	1,302	11.6	8.1	252	664	474	375	99	190	1,276	9.0	7.5	251	584	478	372	106	106	1
10/31-11/1	56.2	1,637	11.5	7.9	203	761	578	496	82	183	1,723	9.2	8.2	287	689	557	441	116	132	
11/ 1- 2	56.2	1,189	12.3	7.4	...	768	512	466	46	256	1,600	8.9	7.4	...	717	502	455	47	215	
11/ 2- 3	56.2	1,224	16.1	11.8	175	381	364	331	33	17	1,506	14.2	11.3	...	390	360	329	31	30	
11/ 3- 4	56.4	1,250	16.4	13.1	199	364	329	280	49	35	1,563	14.1	13.4	...	343	320	295	25	23	
11/ 4- 5	56.2	1,279	18.2	12.9	...	750	544	465	79	206	1,752	14.3	12.9	...	751	533	470	63	218	
11/ 5- 6	56.2	1,248	25.4	14.7	...	731	520	504	16	231	1,804	15.0	14.0	245	740	520	505	15	220	2
11/ 6- 7	56.2	1,182	24.0	15.1	...	764	542	520	22	222	1,566	15.8	14.9	...	702	526	506	20	176	
11/ 7- 8	56.0	1,236	24.5	16.7	...	737	560	510	50	177	1,594	17.9	16.5	211	690	530	490	40	160	
11/ 8- 9	55.8	1,154	22.8	14.7	...	759	550	467	83	209	1,482	17.2	15.0	...	750	560	466	94	190	
11/ 9-10	55.6	1,345	15.5	11.0	...	475	428	337	91	47	1,485	12.0	11.0	...	452	427	356	71	25	
11/10-11	55.6	1,262	14.6	8.6	...	491	388	308	80	103	1,395	9.3	8.9	274	458	379	290	89	79	
11/11-12	55.8	1,256	12.7	8.1	162	565	442	359	83	123	1,430	11.4	8.2	136	499	394	343	51	105	
11/12-13	56.2	1,252	12.7	8.3	207	650	451	410	41	199	1,270	9.5	7.8	208	570	447	390	57	123	3
11/13-14	56.4	1,740	11.3	8.3	228	676	456	422	34	220	1,500	9.8	8.5	230	676	451	427	24	219	
11/14-15	56.4	1,288	11.8	8.2	183	554	462	415	47	92	1,442	9.0	8.1	163	526	433	401	32	93	
11/15-16	56.4	1,265	11.9	8.0	202	525	430	390	40	95	1,486	9.1	8.3	207	504	428	380	48	76	

TABLE 4.—*Data for Patient (Case 21) with Glomerulonephritis*

		Urine as Voided										Protein-Free Urine								
Date, 1934	Body Weight, Kg.	Creatinine, Mg.	Total Nitrogen, Gm.	Urea and Ammonia Nitrogen, Gm.	Amino-Acid Nitrogen, Mg.	Total Sulfur, Mg.	Total Sulfate, Mg.	Inorganic Sulfate, Mg.	Ethereal Sulfate, Mg.	Neutral Sulfur, Mg.	Urine, Cc.	Total Nitrogen, Gm.	Urea Nitrogen, Gm.	Amino-Acid Nitrogen, Mg.	Total Sulfur, Mg.	Total Sulfate, Mg.	Inorganic Sulfate, Mg.	Ethereal Sulfate, Mg.	Neutral Sulfur, Mg.	Period
9/11-12	51.8	987	13.1	10.4	125	1,292	1,192	1,098	94	100	1,880	12.2	10.5	125	1,245	1,180	1,083	97	65	
9/12-13	51.8	995	13.2	10.5	130	1,299	1,187	1,089	98	112	1,950	12.3	10.4	130	1,241	1,157	1,079	78	84	
9/13-14	51.2	1,086	13.4	10.8	131	1,307	1,201	1,110	91	106	2,150	12.6	10.8	131	1,262	1,150	1,072	78	112	1
9/14-15	51.6	903	13.4	10.8	136	1,315	1,210	1,104	106	105	2,090	12.4	10.8	136	1,254	1,162	1,064	98	92	
9/15-16	51.6	1,009	12.9	10.4	128	1,215	1,113	1,023	90	102	1,740	12.2	10.2	128	1,195	1,100	1,002	98	95	
9/16-17	51.6	1,010	12.9	10.3	127	1,231	1,119	1,037	82	112	2,050	12.1	10.3	127	1,165	1,085	1,000	85	80	
9/17-18	52.0	1,034	21.6	18.3	130	1,285	1,195	1,115	80	90	2,080	19.5	18.3	130	1,175	1,095	1,002	93	80	
9/18-19	52.4	1,107	22.0	18.0	132	1,305	1,213	1,123	90	92	2,550	20.9	18.0	132	1,249	1,190	1,105	85	59	
9/19-20	51.4	1,074	24.2	20.3	132	1,322	1,221	1,130	91	101	2,700	21.5	20.3	132	1,180	1,084	1,004	80	96	
9/20-21	51.4	1,085	19.7	16.8	139	1,301	1,206	1,122	84	95	2,010	18.1	16.8	137	1,220	1,125	1,040	85	95	2
9/21-22	51.4	1,160	23.7	19.9	134	1,312	1,227	1,135	92	85	2,500	21.0	19.9	134	1,183	1,098	1,009	89	85	
9/22-23	52.0	1,100	22.9	19.0	133	1,298	1,206	1,116	90	92	2,440	20.3	19.0	133	1,170	1,080	1,002	78	90	
9/23-24	52.0	1,097	22.5	18.5	131	1,284	1,200	1,120	80	84	2,345	20.4	18.5	131	1,181	1,101	1,019	82	80	
9/24-25	51.8	1,114	15.6	12.5	131	1,313	1,222	1,132	90	90	2,350	14.9	12.5	131	1,280	1,190	1,102	88	90	
9/25-26	51.8	1,033	12.1	10.0	134	1,264	1,176	1,091	85	88	2,050	10.9	10.0	134	1,203	1,114	1,029	85	89	
9/26-27	51.6	1,041	12.9	10.2	131	1,252	1,160	1,076	84	92	2,150	12.0	10.2	131	1,205	1,125	1,040	85	80	
9/27-28	51.4	1,044	13.0	10.4	130	1,283	1,198	1,116	82	85	1,725	11.9	10.4	130	1,238	1,149	1,061	88	89	3
9/28-29	51.8	1,068	13.1	10.0	130	1,293	1,206	1,121	85	87	1,940	10.6	10.0	130	1,162	1,087	1,012	75	75	
9/29-30	51.8	1,059	13.1	10.3	135	1,308	1,223	1,143	80	85	2,300	12.0	10.3	136	1,251	1,190	1,105	85	61	
9/30-10/1	52.0	1,064	13.0	10.1	136	1,327	1,242	1,161	81	85	2,000	12.1	10.1	136	1,277	1,197	1,101	96	80	

again in 1932 he had also had gonorrhea. He had always been a heavy drinker, particularly in the last two years. During the last two or three months he had consumed from a pint (473 cc.) to a quart (946 cc.) of whisky a day. He dated his present illness from February 1934, when he noticed the onset of weakness and loss of ambition. During the last two months he vomited every morning. Three hours before the entered the hospital he drank a pint of whisky and one hour later vomited what he estimated to be a quart of blood.

Physical examination showed that he was pale and had a clammy skin. The blood pressure was 106 systolic and 86 diastolic. The spleen was enlarged to percussion. The edge of the liver was felt 9 cm. below the costal margin. The patient had some delusions at night, which a psychiatrist believed were due to alcohol. A blood count showed 2,600,000 erythrocytes. Esophageal varices could not be demonstrated roentgenographically. No lesions were observed in the gastro-

TABLE 5.—*Data for Patient (Case 22) with Cirrhosis of Liver*

Date, 1934	Weight, Kg.	Urine, Cc.	Creatinine, Mg.	Total Nitrogen, Gm.	Urea Nitrogen, Gm.	Amino-Acid Nitrogen, Mg.	Total Sulfate, Mg.	Inorganic Sulfate, Mg.	Ethereal Sulfate, Mg.	Neutral Sulfur, Mg.	Total Sulfur, Mg.	Period
7/31-8/1	67.0	900	1,296	8.3	6.1	165	616	561	55	70	686	
8/ 1- 2	67.2	795	1,324	8.7	6.8	159	618	570	48	75	693	
8/ 2- 3	67.4	690	1,354	8.7	5.5	149	615	564	51	61	676	1
8/ 3- 4	67.6	1,090	1,134	8.3	6.4	149	619	577	42	43	662	
8/ 4- 5	67.8	1,200	1,212	8.3	6.3	149	613	581	32	50	663	
8/ 5- 6	67.4	1,900	1,164	9.5	8.7	155	861	790	71	40	901	
8/ 6- 7	....	1,175	960	12.8	9.9	150	682	614	68	79	761	
8/ 7- 8	67.6	900	1,062	14.8	12.4	150	679	610	69	75	754	
8/ 8- 9	67.8	1,200	1,061	24.2	15.9	151	676	607	69	81	757	
8/ 9-10	68.2	1,118	1,075	18.2	14.7	155	680	612	68	85	765	2
8/10-11	68.2	805	1,055	13.0	10.2	152	661	600	61	80	741	
8/11-12	68.2	1,425	1,060	15.8	13.2	150	685	615	70	71	756	
8/12-13	68.4	1,860	1,147	12.8	10.7	160	782	701	81	70	852	
8/13-14	68.4	1,550	1,149	8.4	7.2	151	655	595	60	50	705	
8/14-15	68.8	1,080	1,065	8.5	6.2	149	627	582	45	46	673	
8/15-16	68.0	1,600	1,064	7.3	5.8	159	769	700	69	91	860	3
8/16-17	68.4	1,675	1,080	11.8	8.7	153	748	688	60	80	828	
8/17-18	68.5	965	1,062	8.8	6.2	151	651	602	49	48	699	
8/18-19	68.2	600	1,062	8.8	6.3	151	644	599	45	48	692	

intestinal tract. Lumbar puncture showed that the fluid was normal. The urine showed no abnormality, and the blood count rapidly returned to normal. The course during the patient's stay in the hospital was uneventful. At the time of his discharge, on August 21, the only abnormal physical sign was the enlargement of the liver, the edge of which could be felt 4 cm. below the costal margin.

OBSERVATIONS AND COMMENT

As can be seen from table 7, our results confirm previous observations as to the retention of nitrogen and urea in nephrosis. Since we were able to confirm these results under the present experimental conditions, in which every possible factor was rigidly controlled, doubt as to technical errors must be excluded from consideration. It is evident also that the earlier observations on the excretion of ingested crystalline urea by a normal subject can be substantiated. In the urine and feces of our normal control we were able to account for all the urea fed

save 0.4 Gm. per day, which is the amount usually stated to be excreted in the sweat. This experiment was carried out in July, and the subject was not in bed, so that this loss in the sweat is entirely reasonable.

TABLE 6.—*Data for Normal Subject*

Date, 1934	Body Weight, Lb.	Urine, Cc.	Creatinine, Mg.	Total Nitrogen, Gm.	Urea Nitrogen, Gm.	Amino-Acid Nitrogen, Mg.	Total Sulfate, Mg.	Inorganic Sulfate, Mg.	Ethereal Sulfate, Mg.	Neutral Sulfur, Mg.	Total Sulfur, Mg.	Period
8/ 8- 9	160	980	1,205	11.6	9.8	163	1,141	1,080	61	65	1,206	
8/ 9-10	160½	1,205	1,199	11.8	10.0	164	1,147	1,085	62	65	1,212	
8/10-11	160	1,276	1,193	11.7	10.0	158	1,149	1,075	74	52	1,201	1
8/11-12	160	1,435	1,191	11.8	10.0	158	1,156	1,091	65	65	1,221	
8/12-13	161	1,210	1,204	12.0	10.2	162	1,140	1,069	71	73	1,213	
8/13-14	160	1,550	1,291	17.7	14.6	155	1,160	1,079	81	72	1,232	
8/14-15	160	1,595	1,222	21.9	18.6	159	1,163	1,095	68	65	1,228	
8/15-16	161½	1,110	1,211	20.4	18.4	159	1,143	1,065	78	63	1,210	
8/16-17	160	1,392	1,205	19.8	18.8	160	1,149	1,089	60	70	1,219	2
8/17-18	160½	1,460	1,206	19.6	18.0	164	1,116	1,051	65	72	1,188	
8/18-19	161	1,510	1,208	19.0	17.9	163	1,145	1,081	54	60	1,206	
8/19-20	162	1,235	1,212	17.9	16.1	162	1,151	1,085	66	69	1,220	
8/20-21	161	1,650	1,226	14.6	12.6	161	1,134	1,067	77	69	1,203	
8/21-22	160	1,190	1,214	13.9	12.0	159	1,148	1,074	74	65	1,213	
8/22-23	159	1,200	1,224	12.5	10.5	160	1,140	1,070	70	71	1,211	
8/23-24	159	1,540	1,200	12.5	10.6	160	1,147	1,088	59	76	1,223	3
8/24-25	160	1,125	1,226	12.7	10.7	162	1,121	1,050	71	78	1,199	
8/25-26	159½	1,481	1,220	11.4	9.4	160	1,123	1,063	60	75	1,198	
8/26-27	159½	1,189	1,201	11.3	9.4	158	1,155	1,075	80	71	1,226	

TABLE 7.—*Details of the Average Daily Nitrogen Balance*

Subject	Period	Days	Nitrogen Intake, Gm.	Nitrogen Output in Urine and Feces, Gm.	Urea Output, Gm.	Nitrogen Balance, Gm.	Urea Balance, Gm.*	Output of Protein Nitrogen, Gm.	Net Nitrogen Balance, Gm.
Nephrosis	1	5	15.6	12.4	7.6	+3.2	±0.0	2.7	+5.9
	2	7	24.8	21.9	14.1	+2.9	+6.5	5.5	+8.4
	3	4	15.6	14.3	9.0	+1.3	+1.4	3.2	+4.5
		3	15.6	12.3	8.2	+3.3	+0.6	3.3	+6.6
Glomerulonephritis	1	6	13.4	14.4	10.5	−1.0	±0.0	0.8	−0.2
	2	7	22.7	23.4	18.7	−0.7	+8.2	2.1	+1.4
	3	1	13.4	16.5	12.5	−3.1	+2.0	0.7	−2.4
		6	13.4	13.8	10.2	−0.4	−0.3	1.1	+0.7
Cirrhosis of liver	1	6	12.9	9.7	6.6	+3.2	±0.0	...	.....
	2	6	21.3	17.6	12.7	+3.7	+6.1	...	.....
	3	1	12.0	13.9	10.7	−1.9	+4.1	...	.....
		6	12.0	10.0	7.0	+2.0	+0.4	...	.....
Normal	1	5	13.0	12.9	10.0	+0.1	±0.0	...	.....
	2	7	22.3	20.6	17.5	+1.7	+7.5	...	.....
	3	5	12.8	14.4	11.3	−1.6	+1.3	...	.....
		2	12.8	12.5	9.4	+0.3	−0.6	...	.....

* The column headed Urea Balance shows the amount of urea nitrogen accounted for, using the excretion of urea in the first period as a base line. The second period is the one during which urea was administered.

Similarly, we were able to recover all the urea fed to the patient with glomerulonephritis. On the other hand, in the patient with nephrosis and in the one with hepatic cirrhosis it was not possible to account for the urea ingested. This leads inescapably to one of two conclusions:

Either the urea ingested is utilized in the economy or the substance is stored in the body as such. The latter denies fundamental physicochemical considerations, in that urea is not demonstrable in the blood. In other words, if urea is retained in the body as such, it should appear in the blood, as it is so readily diffused through cellular membranes. On the other hand, it must be remembered also that urea is an obligatory end-product. If, therefore, it is not stored, it must be excreted in some combined form. This hypothesis gains support from the evident fact that the nitrogen balance is closer than the urea balance. It is also true that this is at the expense of the increased excretion of protein. It has heretofore been assumed, not unnaturally, that the positive nitrogen balance so invariably seen during the nephrosis syndrome is concerned with the replacement of the depleted serum proteins, but this explanation cannot be applied to the patient with cirrhosis, though the relation of the serum proteins is reversed in this condition.[9] The simple replacement of serum proteins by ingested protein seems inadequate to explain the metabolic phenomena in these cases and fails to explain the utilization of urea which seems to occur. That this utilization occurs is suggested by the observation that the total nitrogen balance in the patient with nephrosis seemed closer than the urea balance during the period when urea was ingested; this approach to balance was attained at the expense of an increased excretion of protein. We believe this point to be significant, in that it suggests that the protein excreted may be an end-product of protein metabolism—a faulty one to be sure. This idea receives further support from the fact that this excreted protein is very low in sulfur, unlike the protein in other cases of albuminuria that we have studied and which have been reported elsewhere.[10]

When we consider the sulfur metabolism in these subjects we find that a perfect balance was attained in the normal subject (table 8). Both the patient with nephrosis and the one with cirrhosis showed a strikingly positive balance, while the patient with glomerulonephritis showed an equally important negative balance. The laws governing sulfur balance are probably similar to those regulating nitrogen balance. However, it must be remembered that there is evidence that the sulfur-rich moiety of the protein molecule has a separate metabolism from the sulfur-poor portion.[11] It is evident from these experiments that under pathologic conditions the two may be distinct. The patients with glomerulonephritis showed a negative sulfur balance apart from the protein

9. O'Hare, J. P., and Driscoll, Margaret, in Medical Papers Dedicated to Henry Asbury Christian, Baltimore, Waverly Press, Inc., 1936, p. 639.

10. Grabfield, G. P., and Prescott, B.: Studies on Nitrogen and Sulfur Metabolism in Bright's Disease: VII. Sulfur Content of Urinary Protein, Arch. Int. Med. **57**:1081 (June) 1936.

11. Lewis, H. B.: Physiol. Rev. **4**:394, 1924.

excreted, and this must have come from the sulfur-rich moiety of the protein molecule or from some completely abnormal sulfur product. The latter theory is unlikely, in that the sulfur partition was unchanged from the normal. No effect on the sulfur partition was discernible as a result of the administration of urea (table 9). In all the patients except the one with nephrosis the change in balance was slight, but what change occurred was in a negative direction, which is what would be expected when the diuresis is considered.[12] The changes in the patient with nephrosis were of a much higher order and in the opposite direction; not only the period during which urea was administered but the posturea period as well showed a significant increase of an already

TABLE 8.—*Data for Sulfur Metabolism* *

Subject	Period	Days	Sulfur Intake, Gm.	Sulfur Output in Urine and Feces, Gm.	Sulfur Balance, Gm.	Protein Sulfur, Output, Gm.	Net Sulfur Balance, Gm.
Nephrosis	1	5	1.21	0.70	+0.51	0.06	+0.57
	2	7	1.22	0.67	+0.55	0.02	+0.57
	3	4	1.24	0.60	+0.64	0.05	+0.69
		3	1.24	0.61	+0.63	0.02	+0.65
Glomerulonephritis	1	6	1.02	1.36	−0.34	0.05	−0.29
	2	7	1.02	1.34	−0.32	0.12	−0.20
	3	1	1.02	1.39	−0.37	0.18	−0.19
		6	1.02	1.35	−0.33	0.08	−0.25
Cirrhosis of liver	1	6	1.11	0.77	+0.34		
	2	6	1.12	0.82	+0.30		
	3	1	1.12	0.91	+0.21		
		6	1.12	0.80	+0.32		
Normal	1	5	1.19	1.25	−0.06		
	2	7	1.19	1.24	−0.05		
	3	5	1.20	1.25	−0.05		
		2	1.20	1.23	−0.03		

* These data correspond to the figures shown for the nitrogen metabolism given in table 7.

important retention of sulfur. This may indicate a use of the retained urea in combination with the "extra sulfur" retained during the feeding of urea.

If the sulfur metabolism is intimately bound up with the protein metabolism (and there is no doubt that much if not all of it is), some light may be shed on these findings by a comparison of the excretion of sulfur with that of nitrogen. Indeed it may be possible by this comparison to determine whether these variations are due primarily to a pathologic protein metabolism, since in subjects under normal metabolic conditions and in a good nutritional state the nitrogen-sulfur ratio of the urine approximates that of the food or is even somewhat lower. Con-

12. Hawk, P. B.: Univ. Pennsylvania M. Bull. **18**:1, 1905.

sequently, variations in this ratio in the urine and feces suggest which part of the protein molecule is being metabolized and which is being utilized. From table 10 it will be observed that the patient with nephrosis

TABLE 9.—*The Sulfur Partition Expressed as a Percentage of the Total Urinary Sulfur*

Subject	Period	Days	Total Sulfate	Inorganic Sulfate	Ethereal Sulfate	Neutral Sulfur
Nephrosis	1	5	76	65	11	24
	2	7	79	72	7	21
	3	4	84	70	14	16
		3	78	72	6	22
Glomerulonephritis	1	6	92	86	6	8
	2	7	93	85	8	7
	3	1	93	86	7	7
		6	93	86	7	7
Cirrhosis of liver	1	6	92	85	7	8
	2	6	90	81	9	10
	3	1	92	82	10	8
		6	92	84	8	8
Normal	1	5	95	89	6	5
	2	7	94	89	5	6
	3	5	94	89	5	6
		2	94	89	6	6

TABLE 10.—*The Nitrogen-Sulfur Ratio*

			Nitrogen-Sulfur Ratio				
Subject	Period	Days	Intake	Urine	Protein-Free Urine	Feces	Total Output
Nephrosis	1	5	12.9	17.4	14.8	61.0	17.7
	2	7	20.3	32.2	24.9	26.6	32.7
	3	4	12.6	25.2	21.3	19.5	23.9
		3	12.6	20.3	16.4		20.2
Glomerulonephritis	1	6	13.1	10.4	10.0	15.0	10.6
	2	7	22.2	16.8	18.3	11.8	17.5
	3	1	13.1	11.9	11.6	11.2	11.8
		6	13.1	10.0	8.0		10.2
Cirrhosis of liver	1	6	11.6	12.0	....	19.7	12.6
	2	6	19.0	21.8	....	18.2	21.5
	3	1	10.7	16.9	....	18.2	15.3
		6	10.7	11.8	....		12.5
Normal	1	5	10.9	9.6	....	50.8	10.3
	2	7	18.7	16.0	....	50.1	16.6
	3	5	10.7	11.0	....	50.6	11.5
		2	10.7	9.4	....		10.2

Note the high ratio of the output of the patient with nephrosis.

showed the highest figures in every period and that this is equally true when only the nonprotein portions of the urine are considered. Even higher figures for this value have been previously reported.[1] It should be noted also that the exhibition of urea caused a greater rise in this

ratio in the three patients than in the normal subject. Ordinarily the diuresis produced by urea would make one expect a slight increase in the excretion of sulfur, instead of which one sees by the rise in the ratio with what tenacity these patients held on to sulfur. As a further investigation, it seemed worth while to compare the excretion of inorganic sulfate with the excretion of urea. These two fractions of the sulfur and nitrogen excretion are supposed to represent the end-products of protein metabolism, and such a comparison of the ratios indicates whether the nitrogen-sulfur ratio was an adequate representation of the course of the protein metabolism in these patients and also whether the administration of crystalline urea had any effect on this metabolism. When the nitrogen-sulfur ratio of the food ingested is compared with either the nitrogen-sulfur ratio of the urine or the urea nitrogen-inorganic sulfate ratio, it is evident that only the patient with nephrosis selectively retained sulfur, and it is further evident that the administration of urea called forth a greater relative diminution in the excretion of sulfur in this patient. The relationship of urea nitrogen to inorganic sulfate is a closer index of the food metabolized than the total nitrogen-sulfur ratio, though of course there is a strong parallelism. On the other hand, this means that one is forced to conclude that the protein of the diet is handled in a normal fashion so far as the portion that is excreted is concerned.

Can any further information be obtained from the other sulfur or nitrogen fractions? The neutral sulfur seemed to represent a slightly larger fraction of the total sulfur in the patient with cirrhosis and a considerably larger percentage in the patient with nephrosis, being more than double the normal on the average. The significance of this increase in neutral sulfur is not clear, though variations in this fraction are usually referred to changes in the intermediary protein metabolism. Similar considerations apply to the ethereal sulfates, except that in the patient with nephrosis a striking effect was produced by the administration of urea in a lowering of this fraction. This is difficult to explain, as this fraction is alleged to arise from intestinal putrefaction and to be an index thereof. How urea, an indifferent, completely absorbed substance, can effect the excretion of ethereal sulfate is difficult to imagine unless one is dealing with some sulfur linkage similar to that described by Johnson[13] and conjugated in these patients to ethereal sulfates. As these processes are concerned with the liver, it seems desirable to search further for pathologic processes in this organ in these patients and to recall that the patient with cirrhosis and the one with nephrosis both exhibited positive nitrogen and sulfur balances amounting to retention.

13. Johnson, T. B., cited by Kahn, M., and Goodridge, F. G.: Sulfur Metabolism: A Review of the Literature, Philadelphia: Lea & Febiger, 1926, chap. 35.

As far as we can gather from these experiments, it seems fairly possible to conclude that there are underlying metabolic disturbances affecting particularly the sulfur-rich moiety of the protein molecule in patients with nephrosis and that, as there are certain gross similarities between patients with cirrhosis and those with nephrosis in regard to the nitrogen and sulfur balances, it is desirable to search further for disturbances of the hepatic function in nephrotic patients. That the retention of nitrogen merely compensates for the depletion of serum protein is not tenable, as there is retention beyond the protein nitrogen lost without causing a change in the level of the serum protein. The thought that such retention went to replacing the tissue proteins that possibly had been called on in our patient with nephrosis is untenable, since there was no corresponding gain in weight. The avidity with which such patients retain sulfur suggests that one may be dealing with a primary derangement of the metabolism of the sulfur-rich moiety of the protein molecule or possibly with the intermediary sulfur metabolism. There is slight evidence that the kidney plays a rôle in the metabolism of cystine, and it may be that this mechanism is involved in Bright's disease. On the other hand, the patient with cirrhosis showed retention of sulfur and nitrogen in equal proportions; and it is therefore reasonable to suppose that while part of the mechanism of the retention of sulfur and nitrogen in these two cases may be identical, there is some additional factor involved in nephrosis.

In contrast to the retention of sulfur discussed in the preceding paragraph, how is one to explain the negative sulfur balance in the patient with glomerulonephritis? If nephrosis always occurred as an incident in the course of glomerulonephritis, one might assume that the opposite reactions in the two conditions complement or follow each other. While the effort to retain sulfur appears to extend to the protein of nephrotic patients, the converse cannot be definitely demonstrated of the protein in the patients with glomerulonephritis. It seems to us that the two findings may be manifestations of entirely different mechanisms. It is impossible with the present evidence to explain the findings. Their tabulation in summary will indicate possibly the future attack on this phase of Bright's disease.

Since this is the final report of this series of experiments, it seems desirable to include in the summary all the results obtained. We conclude that the evidence of abnormal protein metabolism suggests that further study of this problem may ultimately yield fruitful practical data.

SUMMARY

Patients with the nephrosis syndrome retain nitrogen and sulfur.[1] They remain in positive nitrogen and sulfur balance, but a larger proportion of sulfur than of nitrogen is retained.

This positive balance is not due to the edema per se,[14] to excess dietary sulfur [15] or to retention in the blood. It extends to crystalline urea.[3]

The neutral sulfur fraction of the urine is increased in nephrosis.

Patients with glomerulonephritis are in negative sulfur balance,[2] but the nitrogen balance is even except for the nitrogen contained in the protein excreted.

The protein excreted in the urine during the nephrosis syndrome is low in sulfur and is not serum albumin.[10]

A patient with cirrhosis of the liver showed a positive sulfur and nitrogen balance but in equal proportions.

CONCLUSION

In the various forms of Bright's disease variations in the excretion of nitrogen and sulfur have been demonstrated which indicate that there are changes in the protein metabolism affecting probably the sulfur-rich moiety of the protein molecule. Such changes may be a fundamental factor in these conditions.

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14. Grabfield, G. P.; Driscoll, M., and Gray, M. G.: Nitrogen and Sulphur Metabolism in Bright's Disease: V. Metabolic Study of a Patient with Edema of Unknown Origin, Arch. Int. Med. **54**:764 (Nov.) 1934.

15. Grabfield, G. P., and Adams, L. G.: Nitrogen and Sulphur Metabolism in Bright's Disease: VI. Effect of Diets Low in Sulphur on the Excretion of Sulphur, Arch. Int. Med. **55**:360 (March) 1935.

ROENTGENOGRAPHIC STUDY OF ORTHOSTATIC ALBUMINURIA BY MEANS OF INJECTIONS OF DIODRAST

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That the pathogenesis of orthostatic albuminuria is poorly understood is attested by recent reviews.[1] The name orthostatic albuminuria is derived from a clinical symptom—the presence of an increased amount of protein in the urine while the subject is erect and its fall to a normal level (clinical absence) when he is supine. The object of this paper is to indicate the importance of determining the anatomic basis for this symptom by means of roentgenograms made after the injection of diodrast. The experience of my colleagues and myself in the first five cases in which this method was applied seems to indicate that orthostatic albuminuria arises from diverse anatomic anomalies and cannot be regarded as a distinct entity.

Two general theories may be considered seriously, the circulatory and the mechanical theory. The circulatory theory explains the anomaly on the following bases: First (*a*) in orthostatic albuminuria the amount of protein excreted varies inversely with the pulse pressure,[2] (*b*) in animal experiments a decrease in the pulse pressure leads to a diminution of the renal secretion and (rarely) albuminuria [3] and (*c*) in normal human subjects the erect posture results in a diminution of the renal secretion.[4] Furthermore, (*a*) there are increases in the concen-

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1. (*a*) Medes, G., and Neemes, M.: Orthostatic Proteinuria, in Berglund, H., and Medes, G.: The Kidney in Health and Disease, Philadelphia, Lea & Febiger, 1935, p. 462. (*b*) Fishberg, A. M.: Hypertension and Nephritis, ed. 2, Philadelphia, Lea & Febiger, 1931, p. 257. (*c*) Volhard, F.: Die doppelseitigen haematogenen Nierenerkrankungen, in von Bergmann, E., and Staehelin, R.: Handbuch der inneren Medizin, Berlin, Julius Springer, 1931, vol. 6, p. 832. (*d*) Hartwich, A.: Die gutartigen Albuminurien, Ergebn. d. inn. Med. u. Kinderh. **38**:44, 1930.

2. Erlanger, J., and Hooker, D. R.: An Experimental Study of Blood-Pressure and of Pulse Pressure in Man, Johns Hopkins Hosp. Rep. **12**:145, 1904.

3. Gesell, R. A.: On the Relation of Pulse Pressure to Renal Secretion, Am. J. Physiol. **32**:70 (May) 1913.

4. White, H. L.; Rosen, I. T.; Fischer, S. S., and Wood, G. H.: The Influence of Posture on Renal Activity, Am. J. Physiol. **178**:185 (Sept.) 1926.

tration of protein in the blood (13 per cent) and in the colloidal osmotic pressure (23 per cent) on standing;[5] (*b*) the glomerular filtration rate varies inversely with the colloidal osmotic pressure,[6] and (*c*) direct observation of glomerular urine of frogs has shown that albuminuria accompanies very slow rates of filtration.[7] Objections to the circulatory theory are that not all subjects with orthostatic albuminuria have a low pulse pressure on standing erect,[8] that patients with aortic stenosis or a low pulse pressure from other causes do not necessarily exhibit albuminuria, that orthostatic albuminuria ordinarily appears before the changes in the osmotic pressure occur and that various investigators have found unilateral albuminuria (usually on the left) on ureteral catheterization.

The mechanical theory explains orthostatic albuminuria (*a*) as related to venous compression by lordosis of the lumbar portion of the spine[9] (but lordosis may be present unassociated with orthostatic albuminuria[10]) or, more definitely, (*b*) as due to compression of the left renal vein by the vertebral column and aorta,[11] the superior mesenteric artery[12] or the angle formed by these two vessels.[13]

Attractive as the unilateral (left) mechanical theory is on anatomic grounds, the direct evidence in its favor is far from convincing. In six cases of orthostatic albuminuria Sonne[11] passed ureteral catheters: none of the patients showed albumin in the urine from the right side, one showed total anuria, three others showed anuria on the left alone and two showed albumin in the urine from the left kidney. Hartwich[14] found bilateral albuminuria in two subjects and albuminuria on the left

5. Youmans, J. B.; Wells, H. S.; Donley, D.; Miller, D. G., and Frank, H.: The Effect of Posture (Standing) on the Serum Protein Concentration and Colloidal Osmotic Pressure of Blood from the Foot in Relation to the Formation of Edema, J. Clin. Investigation **13**:447 (May) 1934.

6. Ni, T., and Rehberg, P. B.: On the Influence of Posture on Kidney Function, J. Physiol. **71**:331 (March 23) 1931.

7. Wearn, J. T., and Richards, A. N.: Observations on the Composition of Glomerular Urine, with Particular Reference to the Problem of Reabsorption in the Renal Tubules, Am. J. Physiol. **71**:209 (Dec.) 1924.

8. Bass, M. H., and Wessler, H.: A Study of the Blood-Pressure in Children Showing Orthostatic Albuminuria, Arch. Int. Med. **13**:39 (Jan.) 1914.

9. Jehle, L.: Die Albuminurie, Berlin, Julius Springer, 1914.

10. Lewison, M.; Freilich, E. B., and Ragins, O. B.: Lordosis as a Cause of Postural Albuminuria, Arch. Int. Med. **42**:440 (Sept.) 1928.

11. Sonne, C.: Beitrag zur Aetiologie der lordotischen orthostatischen Albuminurie, Ztschr. f. klin. Med. **90**:1, 1920.

12. Rieser, W., and Rieser, S. L.: The Etiology of Orthostatic Albuminuria, J. A. M. A. **78**:644 (March 4) 1922.

13. Kristenson, A.: Beitrag zur Kenntnis der Pathogenese der orthostatischen Albuminurie und der Varikozele, Upsala läkaref. förh. **31**:641, 1926.

in only one. Ehrmann [14] studied a subject with edema of the left leg; on catheterization urine from the right kidney was albumin free, and there was anuria on the left. Russell [15] saw two patients (neither catheterized) with edema of the left leg; he concluded from anatomic studies that the left kidney was congested, causing the albuminuria. Vorpahl [16] had a patient with marked scoliosis, lumbar convexity on the left and albuminuria. When the scoliosis was temporarily corrected, the albuminuria ceased. Ureteral catheterization on two occasions yielded normal urine from the left and albuminous urine from the right. Even more indirectly, Rieser and Rieser [12] were able to diminish orthostatic albuminuria in two visceroptotic women (one of whom had undergone excision of the right kidney) by a supportive abdominal corset and drew attention to the aorta-mesenteric artery "pincers."

Kristenson,[13] in an exhaustive study, noted a thrombotic process in the cephalad wall of the left renal vein at the crossing of the superior mesenteric artery in 25 per cent of one hundred and twenty-one subjects at necropsy. The process was evenly distributed among males and females and was not noted in subjects less than 8 years of age. In five instances the left renal vein ran behind the aorta—the wall of one of these veins was the site of a similar but larger thrombotic process where it lay under the aorta. In addition to his necropsy studies, Kristenson (considering the connection anatomically between the left renal and the spermatic vein) examined eight hundred and thirty-six soldiers in the kneeling position (forced lordosis) for orthostatic albuminuria and varicocele on the left side: 26 per cent had a potential varicocele on the left side, 22 per cent had albuminuria and 8 per cent had both. Fifty per cent of those with marked varicocele had orthostatic albuminuria.

METHODS

Five young men exhibiting orthostatic albuminuria but otherwise not selected were studied in recumbent and erect postures roentgenographically after the injection of diodrast. Four of the subjects entered the hospital for the investigation, and the fifth one was studied as an outpatient.

The roentgenographic observations were carried out as follows: After a night's rest in bed each subject was taken to the roentgenologic department in a supine position, diodrast was injected and roentgenograms were taken without permitting a change in the subject's position. The subject then stood up and walked about. After one and one-half hours diodrast was again injected while the subject was erect, and roentgenographic examinations were made. In the first trial of one subject, L. S., events were followed fluoroscopically in both posi-

14. Ehrmann, R.: Orthostatische Albuminurie mit chronischem Oedem des linken Beines, Berl. klin. Wchnschr. **48**:496, 1911.

15. Russell, J. W.: Two Cases of Unilateral Edema with Albuminuria, Lancet **2**:925 (Oct. 27) 1923.

16. Vorphal, K.: Ueber einseitige orthostatische Albuminurie, Berl. klin. Wchnschr. **47**:827, 1910.

tions and confirmed by four roentgenograms. One week later he was studied in the erect position alone by means of ten roentgenograms taken within thirteen minutes after completion of the injection of diodrast. The other four subjects were studied on one occasion each; eight roentgenograms were taken in each position within from eight to twenty minutes after the injection of diodrast. Since J. C. could not enter the hospital, roentgenograms were first made while he was in the erect posture. After he had been lying down for two hours he was examined in the supine position.

RESULTS

With L. S. supine under the fluoroscope, diodrast was seen to appear nine minutes after its injection, in good concentration, simultaneously on the two sides (confirmed by two roentgenograms). With the subject erect diodrast was first seen in the right kidney ten minutes after the second injection, but it was

The Areas of the Shadows of the Kidneys of Five Subjects with Orthostatic Albuminuria *

	Recumbent Position	Erect Position	Change on Standing
L. S.			
Right	53	53	± 0
Left	51	62	+11
K. B.			
Right	53.5 ± 1.2	50 ± 0.9	−3.5 ± 1.5
Left	61.5 ± 0.6	67.8 ± 1.1	+6.3 ± 1.2
O. B.			
Right	101.4 ± 0.8	96 ± 0.9	−5.4 ± 1.2
Left	35 ± 1.1	30.5 ± 0.5	−4.5 ± 1.2
J. P.			
Right	59 ± 0.6	85 ± 0.5	+26 ± 0.8
Left	80 ± 1.0	85 ± 0.8	+5 ± 1.3
J. C.†			
Right	65 ± 0.8	74 ± 0.5	+9 ± 0.9
Left	74 ± 0.6	70 ± 0.4	−4 ± 0.7

* The areas are given in square centimeters, with probable errors.
† This subject was ambulatory. The studies with the subject erect were made first and then those with the subject recumbent.

not seen for twenty minutes on the left. Roentgenograms at that time showed good concentration on the right and a very small amount of the contrast medium on the left. The subject then reclined and diodrast reappeared on the left (seen under the fluoroscope) in two minutes. In the second trial on L. S. made one week later, in the erect position only, diodrast was seen in the first roentgenogram (one minute after injection) in the right kidney only. It was not seen until a sixth roentgenogram (six minutes later) on the left; in succeeding roentgenograms it was seen in small amounts on the left side, but there was never as much as on the right. The right kidney was seen to contain a constant amount of well concentrated diodrast throughout the ten roentgenograms, outlining the pelvis and most of the calices. On the left only a few spots of diodrast were ever seen.

With K. B. supine, diodrast appeared faintly in one minute but in good concentration three minutes after the injection, the same on the two sides, outlining a normal pelvis and calices. With the subject erect, diodrast appeared on both sides within two minutes after injection; but while it quickly reached a heavy concentration on the right (though not as concentrated as when the subject was supine), it was never well seen on the left.

O. B. was found to have a very small left kidney and a large right one. Diodrast appeared bilaterally in three minutes when he was supine and in seven minutes when he was erect. The concentration was about equal bilaterally and was not appreciably affected by the changes in posture.

J. P. was found to have reduplication of the ureter and renal pelvis on the left and a very mobile right kidney. When he was supine, diodrast appeared on both sides in two minutes; when he was erect, in ten minutes. The concentration was about equal bilaterally but was more dense with the subject supine (although two roentgenograms taken in the latter position failed to show the upper part of the pelvis on the left side).

As J. C. was unable to enter the hospital, the first set of roentgenograms was made while he stood and the second set after he had been supine for two hours. Diodrast appeared promptly on each side regardless of the subject's posture;

Fig. 1.—Roentgenogram of L. S. in the erect position. In figures 1 to 5 the patient's left side is to the observer's right.

likewise, posture did not materially affect the final concentration, which was always good. While the subject was standing, the upper outer pole of the left kidney appeared to be somewhat flattened; no other abnormalities were observed.

Assumption of an upright posture was associated with the following descents in the position of the renal shadow: L. S.—right 1 cm. and left 1 cm.; K. B.—right 0 and left 2 cm.; O. B.—right 1 cm. and left 1.5 cm.; J. P.—right 5.5 cm. and left 1 cm.; J. C.—right 0 and left 1.5 cm.

The shadows of the kidneys were outlined on suitably clear roentgenograms, and their areas were measured with a planimeter. In L. S. the outlines were measurable in only one pair of roentgenograms, but in the other subjects the outlines were distinct in most of the sixteen roentgenograms.

The accompanying table presents the results of the measurements, while figures 1 to 5 show the appearance of the roentgenograms.

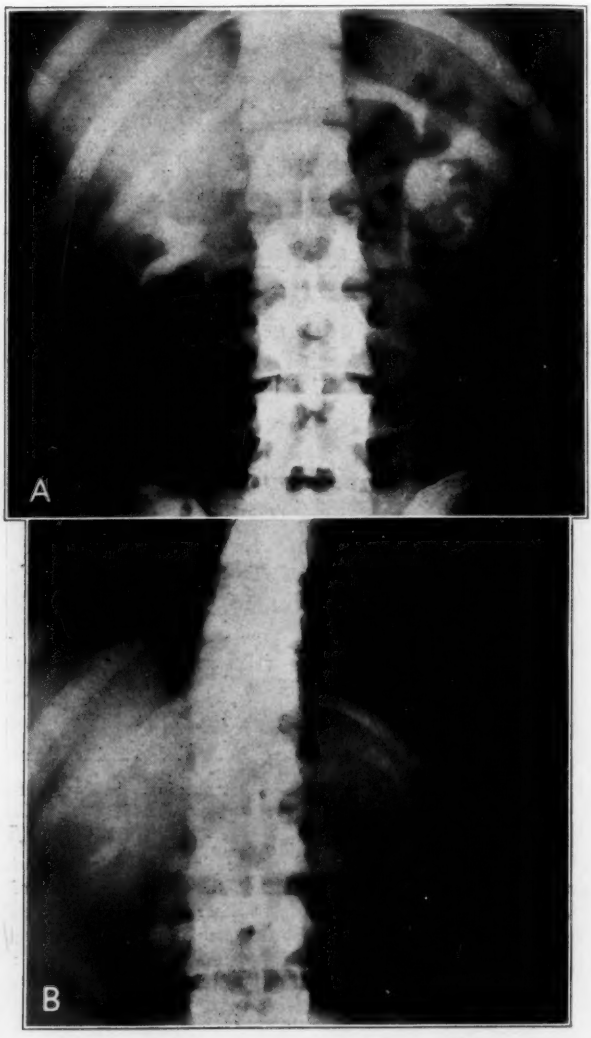

Fig. 2.—Roentgenograms of K. B. in the supine (*A*) and the erect (*B*) position.

The measurements of the areas showed statistically significant changes with changes in posture in every subject. There are two possible interpretations of the changes; (*a*) they were due to rotation of the renal axis with respect to the x-ray beam, or (*b*) they may have had

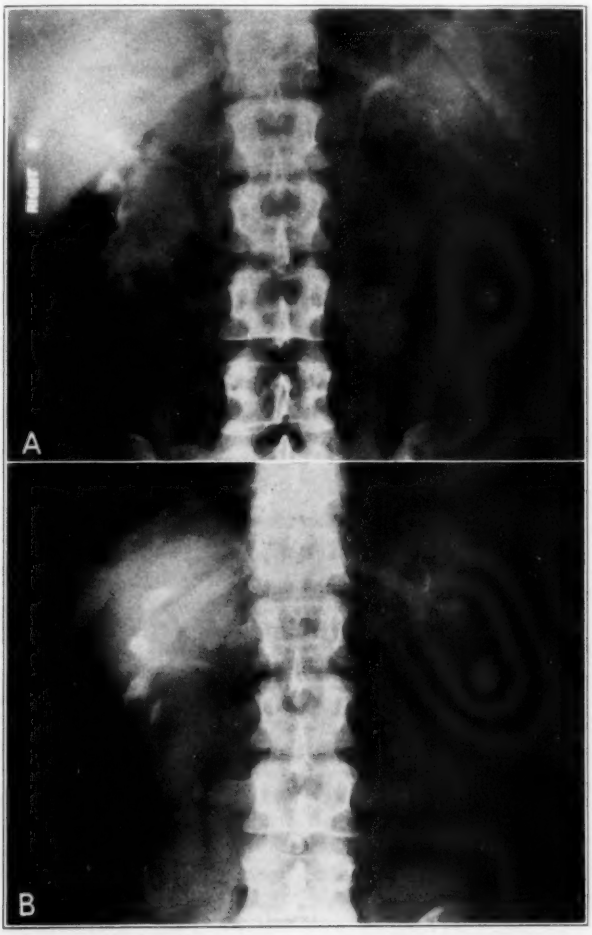

Fig. 3.—Roentgenograms of O. B. in the supine (*A*) and the erect (*B*) position.

physiologic significance; i. e., a decreased area when the subject stood may have been the result of a low pulse pressure, while an increased area may have been brought about by venous stasis in spite of the lower perfusion pressure.

In an effort to interpret the changes in area correctly, further studies at other times were made of J. P. and J. C. A single roentgenogram of J. P. standing gave an area of 90 sq. cm. for each kidney. He was then placed in the supine position, and another roentgenogram was made within thirty seconds. The area

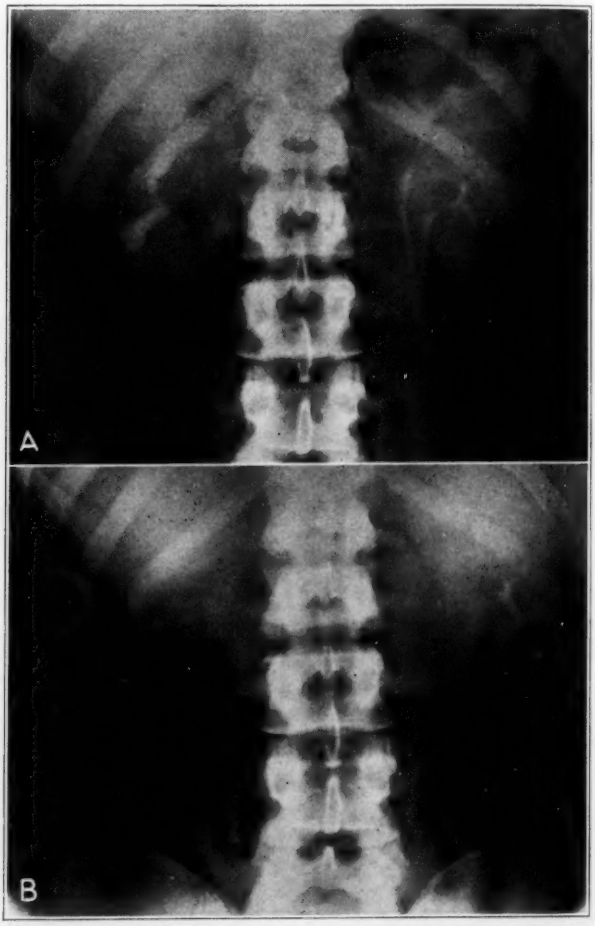

Fig. 4.—Roentgenograms of J. P. in the supine (*A*) and the erect (*B*) position.

of the right kidney was then 59 sq. cm. and that of the left 88. In the case of J. P., therefore, rotation of the renal axis was sufficient to explain the changes observed in the area of the shadow of the right kidney, while changes on the left side may have had physiologic significance. For J. C. roentgenograms were taken three and five minutes after he reclined, following a series of six roent-

genograms taken while he was in the erect position. The area of the left kidney failed to change appreciably; the mean area of the right kidney in the six films taken while the subject was erect was 74 ± 0.5 sq. cm.; after the subject had been supine for three minutes the area was 73 sq. cm., and after five minutes it was

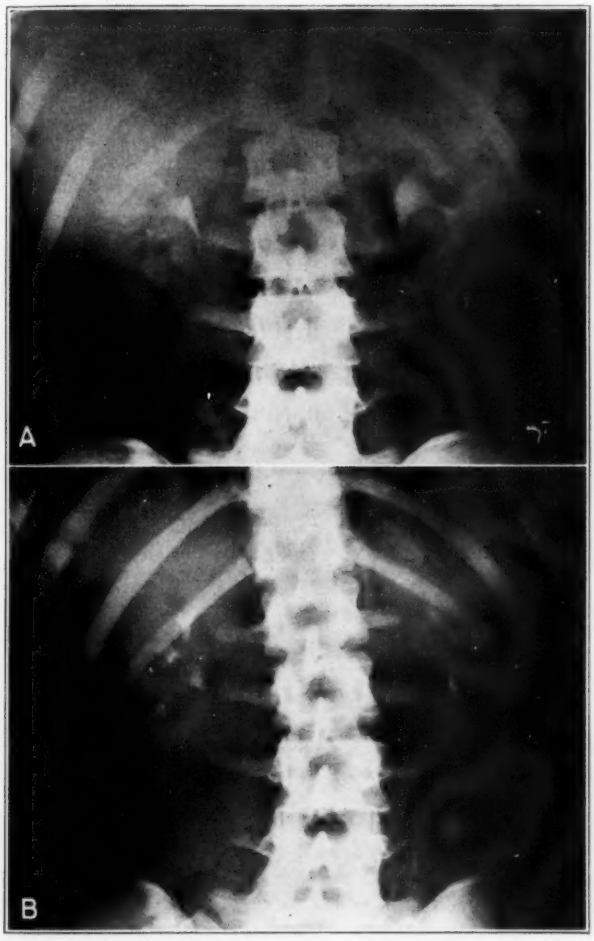

Fig. 5.—Roentgenograms of J. C. in the supine (*A*) and the erect (*B*) position.

68 sq. cm. Conversely, roentgenograms were taken three and five minutes after he had stood up, following the taking of a series of six roentgenograms while he was in the supine position. Again the shadow of the left kidney did not change; the mean area of the shadows of the right kidney in six roentgenograms taken with the subject supine was 65 ± 0.8 sq. cm.; after the subject had been erect

for three minutes it was 66 sq. cm., and after five minutes it was 68 sq. cm. These results suggest, but do not prove, that in J. C. at least the increase in the area of the shadow of the right kidney when he stood was due to actual engorgement of the kidney because of venous stasis and was not due to rotation of the axis.

COMMENT

As far as is known, diodrast has not been used previously in the roentgenographic study of orthostatic albuminuria, even though it has been used as a test of function [17] (see also the references cited by Landis and his colleagues [18]) and its clearance has been studied.[19] The only use of roentgenograms in this connection seems to have been that depicted by Young and Waters,[20] interpreted as showing transitory albuminuria as the result of the crossing of aberrant blood vessels over the ureter.

The results obtained with diodrast may be conveniently grouped into three categories. First, in two subjects (L. S. and K. B.) the left kidney excreted diodrast very poorly, and its shadow became larger with the subject erect. Secondly, in two other subjects (O. B. and J. P.) there were gross anatomic anomalies of the kidneys, but posture did not affect the excretion of diodrast unilaterally to any degree. Finally, no significant abnormalities were disclosed by diodrast in J. C.

An interpretation of the changes in the area of the renal shadows is difficult. By a special technic we were able to show that the large variation in the right kidney of J. P. was due to rotation; the results in the case of J. C. suggested that the changes were related to congestion and not to rotation. Unfortunately, this technic was not in use while L. S. and K. B. were being studied; it would be excellent additional evidence in favor of the mechanical theory if it could be shown that such increases in the area of the left kidney as they exhibited were not caused by rotation of the renal axis.

To summarize, four of five subjects showed definite abnormalities on roentgenographic examination, two showing totally unexpected gross renal defects, presumably congenital in origin. The unilateral (left)

17. Braasch, W. F., and Emmett, J. L.: Excretory Urography as a Test of Renal Function, J. Urol. **35**:630 (June) 1936.

18. Landis, E. M.; Elsom, K. A.; Bott, P. A., and Shiels, E. H.: Simultaneous Plasma Clearances of Creatinine and Certain Organic Compounds of Iodine in Relation to Human Kidney Function, J. Clin. Investigation **15**:397 (July) 1936.

19. Elsom, K. A.; Bott, P. A., and Shiels, E. H.: On the Excretion of Skiodan, Diodrast and Hippuran by the Dog, Am. J. Physiol. **115**:548 (May) 1936. Landis, Elsom, Bott and Shiels.[18]

20. Young, H. H., and Waters, C. A.: Urological Roentgenology, New York, Paul B. Hoeber, Inc., 1928, p. 132, figs. 129-130.

abnormalities in the other two subjects fit in well with the mechanical theory of stasis of the left renal vein, presumably due to compression of the vein between the superior mesenteric artery and the aorta.

It was not possible to catheterize the subjects. In the absence of such direct evidence, one might conclude that the proteinuria was on the left only in L. S. and K. B.; speculation regarding the other subjects is fruitless in the face of the hypoplastic left and hypertrophied right kidney of O. B., the reduplicated left ureter and pelvis and the mobile right kidney of J. P. and the absence of definite findings in J. C.

SUMMARY AND CONCLUSIONS

Five unselected subjects with orthostatic albuminuria were studied roentgenographically after the injection of diodrast.

In two subjects when they were in the supine position diodrast appeared normally in both kidneys; when they were erect it appeared in low concentration in the left kidney, which became larger. In three other subjects posture did not significantly alter the excretion of diodrast unilaterally. One of these subjects had a very small left kidney and a large right one, and a second had a reduplicated left ureter and renal pelvis and a mobile right kidney. No abnormalities were found in the third subject.

Much helpful advice and cooperation were received from the members of the roentgenologic department, especially from Dr. Edward Leef.

THE RENAL LESION IN ORTHOSTATIC ALBUMINURIA

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The results reported in a foregoing paper [1] show that because of the diversity of anatomic renal defects orthostatic albuminuria cannot be regarded as a distinct disease entity. Even the purely clinical definition of orthostatic albuminuria shows a lack of precision. It is incorrect to state that orthostatic albuminuria is a condition characterized by the presence of albumin in the urine while the subject is erect and by the absence of albumin in the urine while he is supine, because albumin (protein) is always present under all conditions. What is really meant is that more albumin is present under certain circumstances than under others. Since this is the case, quantitative methods are essential.

The same five subjects with orthostatic albuminuria who were studied roentgenographically after the injection of diodrast, reported on in the foregoing paper,[1] were further investigated by means of the Addis urea ratio, the Rehberg (creatinine) glomerular filtration rate and the Addis count of the urinary sediment.

It has been stated that tests of the renal function show no impairment in cases of true orthostatic albuminuria, but these tests are usually for the concentration of urea in the blood or the excretion of phenolsulfonphthalein, either of which may fail to show even a gross (50 per cent) reduction of function.[2]

Medes and Neemes [3] have determined the rate of glomerular filtration by the creatinine method for normal subjects and for those with orthostatic albuminuria. Their results showed 171 ± 4 cc., 158 ± 5 cc. and 155 ± 7 cc. per minute for normal subjects, subjects with mild and subjects with severe "lordotic proteinuria," respectively, during thirty minutes of recumbency. The rates were 167 ± 5 cc., 153 ± 7 cc. and 102 ± 9 cc., respectively, for subjects in the lordotic position during

Supported by a grant from the Rockefeller Fluid Research Fund.

From the Department of Medicine, Stanford University Medical School.

1. Rytand, D. A.: Roentgenographic Study of Orthostatic Albuminuria by Means of Injections of Diodrast, Arch. Int. Med., this issue, p. 837.

2. MacKay, E. M., and Rytand, D. A.: Significance of Phenolsulphonphthalein Test of Renal Function, Arch. Int. Med. **60**:131 (Jan.) 1935.

3. Medes, G., and Neemes, M.: Orthostatic Proteinuria, in Berglund, H., and Medes, G.: The Kidney in Health and Disease, Philadelphia, Lea & Febiger, 1935, p. 462.

twenty minutes of standing. That is, the rate of glomerular filtration fell only in those with the more severe orthostatic renal lesions. It is unfortunate that the experimental periods were not longer. While White and his associates [4] found that renal secretion was diminished in normal subjects in the erect position, Van Slyke and his associates [5] found no change in the urea clearance. The latter observers, however, found that in three of twelve nephritic patients with less than 50 per cent of normal clearance, standing (walking) further reduced the standard clearance to from 44 to 67 per cent of its value when the patient was at rest in bed.

METHODS

For the same subjects with orthostatic albuminuria for whom diodrast studies were made and within one or two days of the time of those studies, the Addis urea ratio [6] and the Rehberg creatinine clearance [7] were determined simultaneously over four consecutive hours. The subjects were recumbent for twelve hours prior to and during the first two hours and standing during the second two hours. They were fasting except for 20 Gm. of urea and 5 Gm. of creatinine three hours and one and one-half hours, respectively, before the collection of urine was started. Brisk diuresis was obtained by giving a large amount of water. One subject, J. C., being ambulatory, was erect during the first two hours and supine the succeeding two hours.

Repeated Addis counts [8] of the urinary sediment were made on specimens for from one to eight hours obtained from each of the subjects (fifty-six in five days) for L. S., sixteen in four days for K. B., twelve in four days for O. B., twelve in five days for J. P. and eight in four days for J. C.). Conditions were arranged so that separate specimens were obtained with the subject standing quietly, at ordinary activity, exercising violently (three subjects only) or at rest in bed.

RESULTS

Function Tests.—Table 1 shows that the results of the function tests paralleled closely those obtained roentgenographically after the injection of diodrast. In L. S. and K. B. (in whom it was noted that while they stood diodrast was excreted poorly by the left kidney, which became

4. White, H. L.; Rosen, I. T.; Fischer, S. S., and Wood, G. H.: The Influence of Posture on Renal Activity, Am. J. Physiol. **178**:185 (Sept.) 1926.

5. Van Slyke, D. D.; Alving, A., and Rose, W. C.: Studies of Urea Excretion: VII. The Effects of Posture and Exercise on Urea Excretion, J. Clin. Investigation **11**:1053 (Sept.) 1932.

6. Addis, T., and Watanabe, C. K.: A Method for the Measurement of the Urea-Excreting Function of the Kidney, J. Biol. Chem. **28**:251 (Dec.) 1916.

7. Rehberg, P. B.: Studies on Kidney Function: I. The Rate of Filtration and Reabsorption in the Human Kidney, Biochem. J. **20**:447 (April 26) 1926; II. The Excretion of Urea and Chlorine Analyzed According to a Modified Filtration-Reabsorption Theory, ibid. **20**:461, 1926.

8. Addis, T.: A Clinical Classification of Bright's Disease, J. A. M. A. **85**: 163 (July 18) 1925.

larger) the renal function during the second hour of standing quietly was only one-half as great as the mean function while the subject was supine. On the other hand, in O. B. and J. P. (who had gross anatomic anomalies but who showed no postural change in the excretion of diodrast) posture did not affect the renal function. Finally, in J. C. (in whom there were no definite findings roentgenographically) the renal function while he was in the erect position was 81 per cent of that while he was supine.

The rates of proteinuria were determined during the clearance studies. In O. B. and J. P. the rates were too low to be measured. L. S. excreted protein at the rate of 6 mg. per hour while supine and

TABLE 1.—*Addis Urea Ratio and Glomerular Filtration Rate (Creatinine) in Five Subjects with Orthostatic Albuminuria in Recumbent and Erect Positions*

		L. S.		K. B.		O. B.		J. P.		J. C.*	
Position	Hour	Addis Ratio, % of Normal	Filtration Rate, Cc. per Min.	Addis Ratio, % of Normal	Filtration Rate, Cc. per Min.	Addis Ratio, % of Normal	Filtration Rate, Cc. per Min.	Addis Ratio, % of Normal	Filtration Rate, Cc. per Min.	Addis Ratio, % of Normal	Filtration Rate, Cc. per Min.
Recumbent	1	59	101	100	138	76	149	78†	253	88	210
	2	63	107	107	112	78	169	122	326	91	205
	Mean	61	104	103	125	77	159	122	290	90	207
Erect	3	60	78	70	114	83	149	141	344	81	187
	4	38	56	42	54	85	120	109	279	70	176
Last hour erect in percentage of value when recumbent.....		62	54	41	43	110	75	89	96	78	85
Mean, percentage		58		42		92		92		81	

* The subject was ambulatory. The studies with the subject erect were made before those when he was recumbent.

† Omitted in the calculations because of a lag in reaching the peak of urea-excreting efficiency.

269 mg. while erect; K. B. excreted 4 mg. per hour while supine and 58 mg. while erect, and J. C. excreted 140 mg. per hour while supine and 225 mg. while erect.

Renal Lesions.—In the two instances in which necropsy reports were obtained for patients with undoubted orthostatic albuminuria who died as a result of some other disorder,[9] no significant renal lesions were discovered. Little has been written about the urinary sediment, other than that oxalate crystals, a few red blood cells and "hyaline and even granular casts in small numbers"[10] may be found. As a result, one is

9. Heubner, O.: Die chronischen Albuminurien im Kindesalter, Ergebn. d. inn. Med. u. Kinderh. **2**:567, 1908. Holst, P. F.: Orthostatic Albuminuria and Its Relation to Nephritis, Norsk mag. f. lægevidensk. **13**:1377, 1915; abstr., J. A. M. A. **65**:2206 (Dec. 18) 1915.

10. Fishberg, A. M.: Hypertension and Nephritis, ed. 2, Philadelphia, Lea & Febiger, 1931, p. 257.

prone to think of orthostatic *albuminuria* rather than of an orthostatic *renal lesion.*

Table 2 gives the minimum and maximum intensities of the renal lesions as determined by the Addis sediment count with the subject in bed and standing quietly, respectively. The usual findings with the subject erect approached the maximum given in the table.

Data were obtained for three subjects during violent exercise (running). L. S. excreted only 19 mg. of protein, 21,400 casts, 8,700 red blood cells and 351,000 epithelial cells per hour. J. P. excreted only 166 mg. of protein, 29,200 red blood cells and 292,000 epithelial cells but as many as 175,000 casts per hour. J. C. excreted only 155 mg. of protein and 38,000 red blood cells but as many as 171,000 casts and 152,000 epithelial cells per hour. In brief, the intensities of the renal lesions were less during violent exercise than when the subject stood quietly (compare with table 2).

TABLE 2.—*Rates of Excretion of Protein and Formed Elements in Five Subjects with Orthostatic Albuminuria* *

Rates of Excretion per Hour†	L. S.	K. B.	O. B.	J. P.	J. C.
Protein, mg.....	4 690	2 132	5 69	3 263	12 466
Casts.....	0 90,400 90% granular 10% hyaline	0 46,600 100% granular	0 9,200 80% granular 20% hyaline	0 16,700 100% granular	0 16,700 100% granular
Red blood cells....	0 292,000	0 18,700	0 9,200	0 41,700	4,400 61,200
White and epithelial cells‡	15,000 6,250,000	21,500 933,000	45,000 83,400	11,700 583,000	26,200 92,000

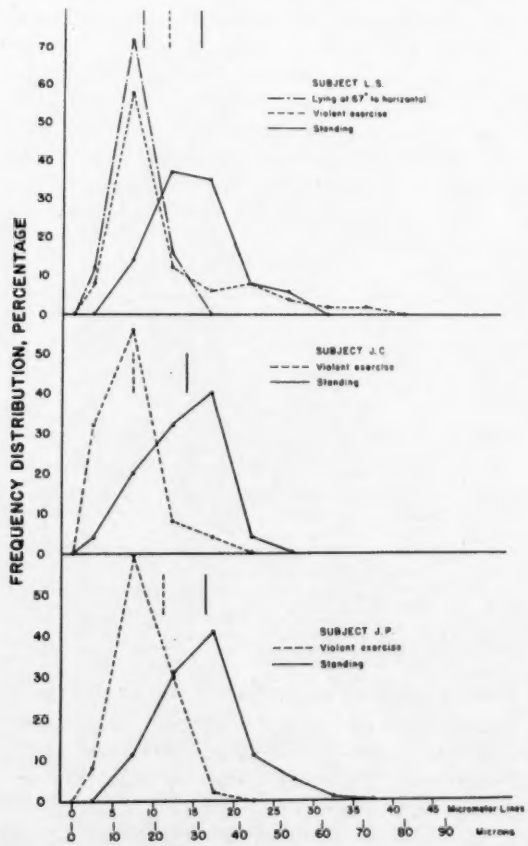
* The upper rows of figures give the minimal findings with the subject in bed. The lower rows of figures give the composite maximal findings with the subjects up and about.
† The upper limits of normal are approximately 8 mg. of protein, 400 casts, 80,000 red blood cells and 80,000 white and epithelial cells per hour.
‡ Almost all were renal tubular epithelial cells.

Congo red was injected intravenously into L. S. at a time when the urine contained 532 mg. of protein per hour; it definitely colored the urine pink and under the microscope could be seen staining the casts. Hartwich [11] previously reported a similar finding.

Such data for the sediment as are given in table 2 (including the healing of the process under favorable conditions) and the escape of congo red are similar to those encountered in cases of any degenerative renal lesion, the outstanding feature here being the extreme rapidity of the degeneration and regeneration. Observations on L. S. indicated that urinary evidences of renal degeneration (protein, casts and tubular epithelial cells) were much less pronounced about one hour after the supine position had been assumed. The onset of the degeneration usually

11. Hartwich, A.: Die gutartigen Albuminurien, Ergebn. d. inn. Med. u. Kinderh. **38**:44, 1930.

began within one hour after the subject stood upright but sometimes did not appear until the second hour. It is generally accepted also that renal degeneration may go on to a diminution of function, as had apparently occurred in L. S. The speed of regeneration is such that at necropsy performed on a subject with orthostatic albuminuria who had



Frequency distribution of the casts according to width in three subjects with orthostatic albuminuria.

been ill in bed for some time before death one might well expect to observe no abnormality on histologic examination of the kidneys.

The width of the casts in the sediment was measured for L. S., J. P. and J. C., for whom both roentgenographic and clearance studies suggested different pathogenic mechanisms of the renal lesions. Figure 1 presents the frequency distributions of the casts by width.

In urine collected while the subject was standing quietly, the mean width (on samples of from 100 to 250 casts) was 30.6 microns for L. S., 31.1 microns for J. P. and 26.9 microns for J. C. In urine obtained shortly after violent exercise the mean width of the casts was only 22.8 microns for L. S., 21.2 microns for J. P., and 14.1 microns for J. C. For L. S., reclining at an angle of 67 degrees to the horizontal for several hours, the mean width of the casts was 16.6 microns. The width of the casts excreted with the subject standing quietly approached that of the broad casts seen in cases of renal failure,[12] while the width of those excreted during exercise or while the subject was lying at an angle of 67 degrees was similar to that of casts from subjects in the early stage of glomerulonephritis.[13] Dilation of the renal tubules by diuresis cannot explain the observed variations in width, for in general the broader casts were accompanied with oliguria. Addis and Oliver[14] have shown that a slow rate of tubular flow is one of the conditions favoring the formation of broad casts.

When the subject was standing, not only were the casts remarkably broad, but almost all were coarsely granular and fragile; during exercise or when the subject was lying at an angle of 67 degrees they were narrow and for the most part hyaline, with embedded droplets of fat or granules. Waxy and cellular casts were rarely seen. These variations suggest that the pathogenic mechanism may be different under the aforementioned conditions. Broad granular casts in the urine of a patient not in uremia should suggest the diagnosis of an orthostatic renal lesion.

COMMENT

Such inadequate tests of renal function as the concentration of urea in the blood and the excretion of phenolsulfonphthalein[2] are of no value in the study of orthostatic albuminuria. All of our subjects had a normal urea content of the blood; and L. S., with a creatinine clearance near the lower limit of normal and an Addis urea ratio only from 59 to 63 per cent of normal (61 per cent on another occasion) while recumbent, showed a perfectly normal identical excretion of phenolsulfonphthalein by the fractional method[15] in both the supine and the erect position.

The orthostatic albuminuria in L. S. was unusually severe; in the absence of other findings, there is no reason for failing to conclude that

12. Addis, T.: Renal Failure Casts, J. A. M. A. **84**:1013 (April 4) 1925.

13. Barnett, G. D., and Barnett, C. W.: Unpublished observations.

14. Addis, T., and Oliver, J.: The Renal Lesion in Bright's Disease, New York, Paul B. Hoeber, Inc., 1931, p. 140.

15. Chapman, E. M., and Halsted, J. A.: The Fractional Phenolsulphonphthalein Test in Bright's Disease, Am. J. M. Sc. **186**:223 (July) 1933.

the diminution of the renal function was due to the orthostatic renal lesion. On the other hand, the reduction in function is not sufficient to place the diagnosis in doubt without other evidence; the final criterion is the *complete* quantitative normality of the urinary sediment while the subject is recumbent. Similarly, O. B., with a hypoplastic left kidney, showed an Addis urea ratio that was only 77 per cent of normal. Conversely, J. P. showed large renal shadows roentgenologically, high rates of glomerular filtration and an Addis urea ratio 122 per cent of normal.

The reduction of the Addis urea ratio and the glomerular filtration rate for L. S. and K. B. when they stood was in accord with the excretion of diodrast, while neither the function test nor the diodrast test showed any significant changes in O. B. and J. P. when they stood. The relatively small reduction of function in J. C. was not correlated with significant changes in the excretion of diodrast. It should be noted that neither O. B. nor J. P. showed any measurable proteinuria during the part of the function test when they were erect.

The pulse pressure of our subjects varied from 10 to 27 mm. of mercury when they were in the erect position, but there was no correlation between the diminution of the pulse pressure and the intensity of the orthostatic renal lesion. Without the use of diodrast, all of our subjects would have shown evidence compatible with the circulatory hypothesis. While a low pulse pressure and hemoconcentration may, theoretically at least, play an incidental rôle in the pathogenesis of orthostatic albuminuria, the demonstration by means of diodrast of unilateral changes following a change in posture in two cases and of gross renal anomalies in two others affords strong confirmatory evidence for the mechanical theory.

The finding of a reduced function by adequate tests and the association with unexpected gross renal anatomic anomalies again bring up the question of the prognosis in cases of orthostatic albuminuria. The prognosis is obviously altered by the nature of the anomalies (such as a predisposition to hydronephrosis or infection) and cannot be as optimistic in all cases as current opinion would have it. Because of the variable conditions found in such a high incidence of our unselected subjects, the prognosis should be based on a roentgenographic study by means of diodrast and rigid tests of the renal function in each case.

These findings further suggest that true orthostatic albuminuria should not be classed with "benign" albuminuria which is said to disappear as the subject grows older.

CASE REPORTS

Leslie S., aged 15, had never had hematuria, albuminuria, edema, scarlet fever or severe tonsillitis. Headaches for eighteen months and an attack of syncope caused him to go to a physician one month before the present study was made.

Albuminuria was found in an afternoon specimen, and a diet was prescribed. He appeared to be perfectly healthy (172 cm. tall, weighing 58.1 Kg.). The pulse rate was 60, and the blood pressure was 100 systolic and 70 diastolic. The fundi and heart were normal, the radial pulse was soft, the kidneys were not palpable and no edema or varicocele was noted. The back showed slight lumbar scoliosis, with convexity to the left, but no abnormal lordosis. The blood count, stools, basal metabolic rate and sedimentation rate were normal. The Wassermann reaction was negative. Eighty per cent of the injected congo red remained in the serum after one hour. The concentration of the plasma protein was 6.3 per cent; the cholesterol content, 161 mg. per hundred cubic centimeters, and the urea content (six hours after the administration of 20 Gm. of urea), 45 mg. per hundred cubic centimeters.

Kenneth B., aged 19, gave no history of significance. Albuminuria was discovered during a routine examination at school two years prior to the present study, and it diminished or disappeared during rest in bed. The patient was asked to enter the hospital for study, as a diagnosis of orthostatic albuminuria had been made nine months previously. He appeared to be well (170 cm. tall, weighing 58 Kg.). The pulse rate was 70, and the blood pressure was 115 systolic and 85 diastolic. The fundi and the heart were normal, the radial pulse was soft, the kidneys were not palpable and no edema or varicocele was noted. Lumbar lordosis was marked but not pathologic. The blood count and stools were normal. The concentration of urea was 27 mg. per hundred cubic centimeters of blood. The Wassermann reaction was negative.

Odell B., aged 34, gave no past history of significance, except that the results of a urinalysis were normal four years previously and an ache in the lower part of the back was made worse by an injury nine years before. Albuminuria was discovered in the course of a routine examination six weeks before the present study was made. The subject appeared to be well (173 cm. tall, weighing 74.3 Kg.). The pulse rate was 76, and the blood pressure was 125 systolic and 80 diastolic. The fundi and heart were normal, the radial pulse was soft, the right kidney was barely palpable and no edema or varicocele was noted. The lumbar portion of the spine lacked normal lordosis. The Wassermann reaction was negative. The concentration of urea was 28.8 mg. per hundred cubic centimeters of blood.

John P., aged 18, gave no past history of significance, except for the normal results of urinalysis four years before the present study was made. Albuminuria was discovered during a routine examination two years before his admission to the hospital. It decreased during rest in bed but increased when normal activity we resumed. Rest in bed was again prescribed and resulted in a diminution of the proteinuria. The subject appeared to be well (183 cm. tall, weighing 74 Kg.). The pulse rate was 75 and the blood pressure 130 systolic and 75 diastolic. The fundi and heart were normal, the radial pulse was soft, the kidneys were not palpable even when the patient was erect and no edema or varicocele was noted. No exaggeration of lumbar lordosis was present. The concentration of urea was 36.1 mg. per hundred cubic centimeters of blood.

John C., aged 20, gave no significant past history. Albuminuria was discovered one month before his entry, following a febrile illness due to involvement of the respiratory tract. A special diet and restriction of activity were prescribed. He appeared to be well (175 cm. tall, weighing 61.8 Kg.). The pulse rate was 88, and the blood pressure was 150 systolic and 80 diastolic. The fundi and heart were normal, the radial pulse was soft, the kidneys were not palpable and no edema or varicocele was noted. There was no exaggeration of lumbar lordosis

but there was slight scoliosis to the left. The basal metabolic rate was normal, and the concentration of urea was 25.3 mg. per hundred cubic centimeters of blood.

SUMMARY AND CONCLUSIONS

The same five subjects with orthostatic albuminuria who had been studied roentgenographically after the injection of diodrast were studied with regard to the Addis urea ratio, the Rehberg glomerular filtration rate and the Addis count of the urinary sediment.

In the two subjects in whom unilateral changes related to posture were revealed roentgenographically, the Addis urea ratio and the glomerular filtration rate fell in the second hour with the subject erect to approximately one-half the original level with the subject recumbent. In one of these subjects, who had unusually severe albuminuria, the results of the function test were diminished even when he was supine. In the two subjects with gross anomalies, posture did not affect the renal function. In the fifth case there was a 20 per cent fall in the renal function when the subject stood.

In these cases, in addition to proteinuria, standing erect results in the appearance of large numbers of renal epithelial cells and broad granular and hyaline casts in the urinary sediment, a small increase in the red blood cell count occurs inconstantly and congo red escapes into the urine. In brief, there is a transitory renal degenerative lesion.

ABSORPTION OF FAT FROM THE ILEUM IN HUMAN BEINGS

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There have been a large number of reports on the absorption of fat from an isolated intestinal loop in animals, but apparently there is no record of similar observations for human beings. Recently, an opportunity to make such studies was presented by a patient who had accidentally acquired a temporary Thiry fistula of the middle portion of the ileum during treatment for strangulated femoral hernia.

REPORT OF A CASE

History.—A man aged 50 was admitted to the hospital with a strangulated femoral hernia on the left side. At operation, owing to the patient's poor condition and to the fact that the strangulated loop of bowel was gangrenous, resection was not carried out, *Vorlagerung* being performed instead. A tube was inserted into the proximal loop, and a fistula was allowed to form. After four weeks reoperation was performed. Through an abdominal incision both the proximal and the distal loop involving the fistula were divided, and the ends were closed. A side to side anastomosis was then made to restore the continuity of the intestine (fig. 1). At this point the patient's condition became very poor; so the two limbs of the resected loop were left intact, to be removed later. The result was that an afferent and an efferent loop, each about 8 inches (20 cm.) long and opening just below the left inguinal ligament, were left intact, together with the blood and lymph supply.

Experimental Procedure.—Observations were subsequently carried out to determine the rate of absorption of fats from the ileum, both in the absence and in the presence of various pure bile acids.

Oleic acid and olive oil were injected into the efferent loop, and the amount of resorption was estimated for various periods. In some of the observations pure bile acids also were added. In order to produce an efficient closure of the intestinal loop, a special apparatus was constructed (fig. 2). About 6 inches (15 cm.) of a number 12 catheter was passed through a flat rubber pad, 2 by 2 inches (5 by 5 cm.) square. One inch (2.5 cm.) below the rubber pad, a balloon of condom rubber was constructed to encircle the catheter. A piece of fine catheter (number 24) was attached to the balloon for purposes of inflating it. This also passed through the rubber pad. To close off the intestinal loop, the catheter was inserted up to the rubber pad. The balloon was then inflated, and its distention tended to push it farther into the loop. The result was that the rubber pad was

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forced firmly against the opening, which was constricted, owing to its passage underneath the inguinal ligament. The efferent loop was used, since the direction of the peristaltic action tended to keep the tube in place.

Observations were always carried out in the same manner and at the same time of day. The material was injected at 10:30 a. m. and removed either at 1:30 p. m. or at 4:30 p. m. As a result, only a limited number of observations could be carried out before the patient underwent the final stage of the operation —the removal of the isolated intestinal loop. At operation and on histologic section the bowel was observed to be normal, being neither distended nor inflamed.

Two hundred and fifty milligrams of gelatin was dissolved in 10 cc. of water. To this was added 1 or 3 Gm. of oleic acid or olive oil, and the emulsion was made up to 20 cc. To make up a solution containing bile acids, various amounts of pure cholic or deoxycholic acid were dissolved in 5 cc. of water, an equivalent amount of normal sodium hydroxide being used. This solution was then mixed

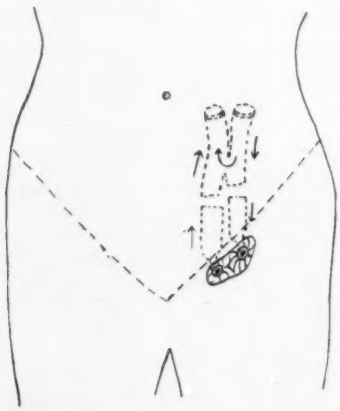

Fig. 1.—Diagram illustrating how two isolated loops of ileum were present after the second operation on the patient. The efferent loop was used for experimental purposes.

with the gelatin solution, the fat was added and the emulsion was made up to 20 cc. This material was then injected into the isolated loop and the tube clamped. At the end of three or six hours the contents of the loop were aspirated with a syringe, and the volume of fluid withdrawn was measured. In order to obtain any material adherent to the mucosa, the loop was washed with 20 cc. of saline solution. The fat content of the saline washings was added to the total fat content. The total lipid content was estimated in each instance. Either a measured part or the total amount of the recovered fluid was precipitated with 100 cc. of Bloor's alcohol-ether mixture, and the filtrate was dried to constant weight on the steam bath.

Results.—Secretion of Intestinal Loop: A catheter was placed in the efferent loop, and the intestinal secretion was allowed to drain for three hours. Ten cubic centimeters of milky white fluid was obtained. On analysis this was found to contain 94 mg. of lipid (9.4 mg. per cubic centimeter).

Intestinal Secretion Under Experimental Conditions: The tube previously described (fig. 2) was introduced into the efferent intestinal loop, and the balloon was blown up, thereby sealing the opening. Twenty cubic centimeters of saline solution containing 250 mg. of gelatin in solution was injected, and the tube was closed. At the end of six hours the contents of the loop were aspirated, and the loop was washed with 20 cc. of water. Two experiments were carried out. In the first test 20 cc. of fluid containing 405 mg. of lipid was recovered, and in the second 22 cc. containing 462 mg. was obtained. In each case the fat content of the washings was included in the total fat content. At the end of six hours the intestinal fluid contained 21 and 20 mg., respectively, of lipid per cubic centimeter (experiments 2a and 2b).

Immediate Recovery of Fat Injected into the Intestinal Loop: After the loop had been carefully washed out with saline solution, four experiments were carried out. Twenty cubic centimeters of solution containing 250 mg. of gelatin and 3 Gm.

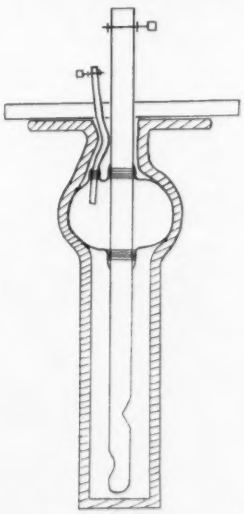

Fig. 2.—Diagram of the apparatus used for injecting fluid into the isolated intestinal loop. Note that the balloon on being inflated tends to pull away from the surface, since the fistulous opening is very narrow. As a result, the flat rubber pad is pressed firmly against the opening.

of either olive oil or oleic acid in the form of an emulsion was injected into the loop and then immediately withdrawn. In each case the loop was washed out with 20 cc. of saline solution. The fat content of the washings was added to that of the main volume of the fluid withdrawn. As can be seen in the accompanying table (experiments 3a, 3b, 3c and 3d), injected material was recovered practically quantitatively (95.7 to 104 per cent).

Recovery of Fat After Three or Six Hours: Either 1 or 3 Gm. of oleic acid or olive oil emulsified with gelatin to a volume of 20 cc. was allowed to remain in the loop for a period of three or six hours. As can be seen from the accompanying table (experiment 4), the volume of fluid recovered tended to be small. The percentage of loss was approximately the same whether the contents were

withdrawn at the end of three or of six hours or whether 1 or 3 Gm. of fat was injected. The average apparent recovery was 30 per cent.

Recovery of Fat After Injection of Bile Acid Alone: After the injection of bile acid alone (experiment 5) there was a large excretion of fluid over a period

Results of Various Experiments

Experiment	Substance Injected	Amount, Mg.	Time Before Withdrawal, Hours	Volume of Fluid Recovered, Cc.	Lipid Recovered, Mg.	Percentage of Lipid Recovered
1	Intestinal secretion	.....	3	10	94	....
2a	Gelatin	250	6	22	462	....
2b	Gelatin	250	6	20	405	....
3a	Oleic acid	3,000	0	20	2,871	95.7
3b	Oleic acid	3,000	0	20	3,031	100.4
3c	Olive oil	3,000	0	20	3,149	104.0
3d	Olive oil	3,000	0	20	2,938	97.9
4a	Oleic acid	1,000	3	5	316	31.6
4b	Oleic acid	1,000	3	12	378	37.8
4c	Olive oil	1,000	3	5	352	35.2
Average						34.9
4d	Olive oil	1,000	6	2	288	28.8
4e	Olive oil	1,000	6	2	155	15.5
Average						22.4
4f	Oleic acid	3,000	0	15	1,796	60.0
4g	Oleic acid	3,000	6	10	759	26.3
4h	Olive oil	3,000	6	2	236	10.0
4i	Olive oil	3,000	6	2	867	28.9
4j	Olive oil	3,000	6	9	680	22.7
Average						29.6
5a	Deoxycholic acid	300	6	100	1,411	....
5b	Cholic acid	300	6	15	401	....
5c	Cholic acid	300	6	60	1,364	....
6a	Oleic acid Cholic acid	3,000 50	3	17	1,350	45.0
6b	Oleic acid Cholic acid	3,000 50	3	15	521	17.4
Average				16		31.2
6c	Oleic acid Glycocholic acid	3,000 50	3	10	577	19.2
6d	Oleic acid Glycocholic acid	3,000 50	3	10	724	24.2
6e	Olive oil Glycocholic acid	3,000 50	3	26	636	21.2
Average				15		21.2
6f	Oleic acid Deoxycholic acid	3,000 50	3	26	720	24.0
6g	Oleic acid Deoxycholic acid	3,000 50	3	34	2,582	86.1
6h	Olive oil Deoxycholic acid	3,000 50	3	40	1,514	51.5
6i	Olive oil Deoxycholic acid	3,000 50	3	20	863	28.8
Average				30		47.4
6j	Oleic acid Deoxycholic acid	1,000 300	3	27	563	56.3
6k	Oleic acid Cholic acid	3,000 300	6	95	1,907	63.6
6l	Olive oil Deoxycholic acid	3,000 300	6	140	3,842	124.7
6m	Oleic acid Deoxycholic acid	3,000 300	6	70	3,583	119.4

of six hours. In the presence of deoxycholic acid there was a much greater excretion of intestinal juice than in the presence of cholic acid. The second experiment with cholic acid was performed the day after the first experiment. As can be seen the yield was four times as great both in volume of fluid and in total amount of fats.

Injection of Fat and Bile Acids: Experiments 6a to 6m show the results of the injection of fat and bile acid. The injection of deoxycholic acid with fats resulted in the largest secretion of fluid and in the recovery of the largest amount of fat. In fact, when 3 Gm. of fat together with 300 mg. of deoxycholic acid was injected and left for a period of three hours, more fat was recovered than was originally injected. When 50 mg. of cholic or glycocholic acid was injected with 3 Gm. of fat and left for three hours, the percentage of recovery was 31.2 and 21.2, while the volume recovered was 16 and 15 cc., respectively. When 50 mg. of deoxycholic acid was injected with 3 Gm. of fat and left for three hours, 47.4 per cent was recovered, while the volume of fluid averaged 30 cc. When 300 mg. of cholic acid was injected with 3 Gm. of fat and left for a period of six hours, 63.6 per cent of the fat was recovered, while the volume was 95 cc. If deoxycholic acid was used instead of cholic acid in the same quantities, 122 per cent was "recovered," while the volume averaged 120 cc.

COMMENT

Although general conclusions cannot be drawn on observations limited to one case during a short space of time, they are of some interest because of their consistency and because they appear to be the first ones made directly on the intestine of a human being.

It is well known that the small intestine secretes a fluid containing a considerable amount of fat.[1] In this case the secretion from the non-obstructed intestine contained 0.94 per cent of lipids. This figure includes the fat content of the large number of lymphocytes normally present in the intestinal secretion. Under the experimental conditions obtaining here, with the open end of the loop closed, about 21 cc. of fluid was recovered in six hours. This fluid contained 433 mg., or about 2 per cent of fat. It is impossible to say whether this fat was a transudate from the blood or an actual secretion. Since the type of fat in the stool is similar to that found in the blood and in fat depots,[2] the inference is that it was a transudate. In that case the amount and rate of excretion of fat into the intestinal lumen should depend on the relative percentage of fat in the circulating blood as compared with the concentration of fat in the intestine. However, since the process by which fat passes through the intestinal mucosa is unknown, it is impossible to state whether the concentration of fat either in the blood or in the intestinal lumen has any influence on the secretion or absorption of fat.

The experiments indicate that olive oil and oleic acid are readily absorbed from the middle portion of the ileum in human beings in the absence of bile acids. Whether the amount of fat recovered at the end of three or six hours is an unabsorbed portion of the injected material or is the result of intestinal secretion has not been determined in these

1. Sperry, W. M., and Angevine, B. W.: Lipid Excretion: IX. The Secretion of Lipids into the Intestine, J. Biol. Chem. **96**:769, 1932.

2. Eckstein, H. C.: Fatty Acids in Subcutaneous Fat of Man, J. Biol. Chem. **64**:797, 1925.

experiments. In considering experiments 4a to 4j, with the exception of experiment 4f, most of the figures for the amount recovered are not far off from the amount of fat excreted into the intestine under the experimental conditions. In other words, the total amount of fat injected may have been completely absorbed, while the amount recovered may have been due to intestinal secretion.

The effect of bile acids is very difficult to interpret. The large amount of intestinal juice excreted when bile acids alone were injected (experiments 5a to 5c) may have been due either to irritation of the mucosal cells or to a physical effect of the bile acids on the mucosa. Bile acids are apparently adsorbed on the surface of the mucosal cells.[3] However, the fat content of the fluid (2.1 per cent, average) was essentially similar to that of the secretion in the absence of bile acids. The action of the bile acids in these experiments was to increase the volume but not the fat content of the intestinal secretion. This increase in volume therefore appears to be due to irritation. This may explain the varying results in the two experiments with cholic acid (5b and 5c). These experiments were performed on successive days, and the irritation produced by the first experiment (5b) may have amplified the irritative effect of the second experiment, thereby increasing fourfold both the volume and the fat content of the intestinal fluid. Experiments 6f and 6g gave a similar result. These were performed on successive days, and the recovery of fat in 6g was almost four times as great as in 6a. Similar findings have been reported by Croner [4] and Gumilewski.[5]

When fat was injected together with small amounts of bile acids, the recovery of fat in general did not differ markedly from the amount recovered after the injection of fat alone. The volume of the recovered fluid was on the average almost three times as great. When large amounts of bile acids were injected together with fat, the volume of intestinal secretion was tremendously increased, in one case up to 140 cc. The effect of a large amount of deoxycholic acid is well illustrated in experiments 6l and 6m, in which more fat was recovered than was injected. The injection of 300 mg. of deoxycholic acid alone (5a) resulted in an excretion of 1.4 Gm. of fat in six hours. In experiments 6l and 6m 3 Gm. of fat was injected, together with 300 mg. of deoxycholic acid. By adding the excretion of fat produced by the action of the deoxycholic alone, there was a total of 4.4 Gm. of fat actually present in the intestinal loop. In these experiments the recovery of fat averaged

3. Verzár, F., and von Kúthy, A.: Die Bedeutung der gepaarten Gallensäuren für die Fettresorption: IV, Biochem. Ztschr. **230**:451, 1931.

4. Croner, W.: Versuche über Resorption von Fetten im Dünndarm, Biochem. Ztschr. **23**:97, 1909.

5. Gumilewski: Ueber Resorption im Dünndarm, Arch. f. d. ges. Physiol. **39**:556, 1886.

3.7 Gm. Therefore, 0.7 Gm. of fat was actually absorbed during a period of six hours. By stimulating the excretion of fat the result of the presence of a large amount of deoxycholic acid in the ileum in this case was to prevent the absorption of fat.

The difficulty of interpreting such results is well illustrated by a short review of some of the literature. Bloor, Sperry and their co-workers [6] have shown that in animals the stool lipids are excreted in consistent amounts and are of uniform type, regardless of the diet. Krakower [7] demonstrated that the same holds true in human beings. Moreover, according to Eckstein,[2] the fecal lipids are apparently similar in composition to those in the fat depots in each species. Accordingly, it appears that fecal lipids represent an excretion of the blood into the small intestine.[1] It therefore follows that all experiments of the type in which the intake is compared either with the fecal output or with the output of an isolated intestinal loop yield results which may be falsely interpreted. The amount of absorption of a measured intake cannot be estimated by analyzing the stool, since the lipids in the stool are completely independent of the intake. If bile is completely diverted from the intestinal tract, absorption of dietary fat is greatly decreased, but at the same time the endogenous excretion of fat is greatly increased, since even with a fat-free diet the stools in cases of complete biliary obstruction are fatty and bulky.

The same factors must be considered in interpreting experiments that utilize an isolated intestinal loop. The amount of fat recovered at the end of a period of time represents not only the material that has not been absorbed but also the lipid that has been excreted during that period.

This confusion in interpretation is well exemplified in early experiments on isolated loops of small intestine in animals. Von Fürth and Schutz [8] found that sodium oleate and stearate were poorly absorbed by cats in experiments covering periods of seven or eight hours. The results were variable, although olive oil apparently could be absorbed to an extent of over 50 per cent. The addition of bile apparently had little effect. Croner [4] showed that neutral fats are best absorbed in the

6. Hill, E., and Bloor, W. R.: Fat Excretion, J. Biol. Chem. **53**:171 (July) 1922. Holmes, A. D., and Kerr, R. H.: Ether Extract of Feces, ibid. **58**:377 (Dec.) 1923. Sperry, W. M., and Bloor, W. R.: Fat Excretion: Quantitative Relations of Fecal Lipids, ibid. **60**:261 (June) 1924. Sperry, W. M.: Lipid Excretion; Further Studies of Quantitative Relations of Fecal Lipids, ibid. **68**: 357 (May) 1926.

7. Krakower, A.: Fecal Fat and Its Relation to Fat in the Diet, Am. J. Physiol. **107**:49 (Jan.) 1934.

8. von Fürth, O., and Schutz, J.: Ein Beitrag zur Methodik der Versuche über Fettresorption aus isolierten Darmschlingen, Beitr. z. chem. Physiol. u. Path. **10**:462, 1907.

lower end of the small intestine. He stated the opinion that the various portions of the small intestine vary both qualitatively and quantitatively in their ability to absorb fats. Apparently in the lower end of the small intestine in animals fats are absorbed to an extent of 50 per cent.

Plant,[9] Verzár and von Kúthy [3] and Riegel and his co-workers [10] have shown that the addition of bile salts greatly increases the resorption of fats from the small intestine in animals.

However, in interpreting all these results three factors must be considered: (1) the situation of the isolated loop, since the lower end of the small intestine seems to absorb fats much more readily than the upper end; (2) the duration of the experiment, since the residual fat is the sum of the unresorbed portion plus the amount excreted during the period of the experiment, and (3) the frequency of the experiments—both Croner [4] and Gumilewski [5] showed that if the loop is left alone for several days the resorption of fat is decreased in the next experiment.

CONCLUSIONS

Observations on the absorption of fat from the middle of the ileum in one human subject showed the following facts:

In a human being the ileum secretes a fluid which contains about 2 per cent of lipids.

The presence of bile acids increases the volume of the secretion, while its lipid concentration remains unchanged.

Olive oil and oleic acid are absorbed from the ileum even in the absence of bile acids.

Bile acids in small amounts have apparently no effect on the rate of absorption of fats from the ileum.

Deoxycholic acid in large amounts increases the volume of the excretion and so tends to reduce the rate of absorption of fat.

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9. Plant, O. H.: Experiments on the Absorption of Fat from an Isolated Loop of Small Intestine in Healthy Dogs, Am. J. Physiol. **23**:65, 1908.

10. Riegel, C.; Elsom, K., and Ravdin, I. S.: The Influence of Sodium Taurocholate, Hepatic Bile and Gall-Bladder Bile upon the Absorption of Oleic Acid from the Small Intestine, Am. J. Physiol. **112**:669 (Aug.) 1935.

SIMMONDS' DISEASE (ANTERIOR HYPOPHYSIAL INSUFFICIENCY)

REPORT OF TWO CASES WITH AUTOPSY

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Because of the current interest in diseases of the endocrine glands and because of the comparative sparsity of reports of cases of Simmonds' disease with autopsy, the following cases are placed on record. There is included also a comparison of some of the effects of the glandular deficiency of Simmonds' disease and of the glandular hyperfunction of acromegaly.

REPORT OF CASES

CASE 1.—A 51 year old housewife was admitted to the Cleveland City Hospital on April 10, 1935, in coma.

Clinical History.—The clinical history was obtained from the records of the University Hospital Dispensary, where the patient was first seen on June 8, 1933. She complained then only of pain and stiffness of the knees, which were worse after disuse and improved with exercise. These symptoms began three years previously, after six months of convalescence from a difficult delivery. The menses, which had been normal, had stopped, and the patient had lost 20 pounds (9 Kg.). She had been married for eight years and had one other child, aged 7 years, who was delivered by cesarean section. Physical examination revealed a small healthy-looking woman weighing 109 pounds (49 Kg.). The temperature was 37.4 C. (99 F.). The teeth were lacking, the eyebrows, eyelashes and hair of the head were thin and no axillary or pubic hair was noted. The clinical diagnosis was arthritis, alopecia and malnutrition.

One cubic centimeter of a preparation of the anterior lobe of the hypophysis [1] weekly and hydrotherapy were advised. The patient reported irregularly and received only 20 cc. of the hypophysial preparation in nine months. Fine pubic and axillary hair appeared, she gained 3 pounds (1.5 Kg.) and the condition of the knees improved. On March 1934 the temperature of 36 C. (96.8 F.) aroused further investigation. The patient admitted chilliness and anorexia. The pulse rate was 78, and the blood pressure was 130 systolic and 80 diastolic. Pelvic examination revealed excessive postmenopausal atrophy for the patient's age. The basal metabolic rate was —33. An electrocardiogram showed an inverted T wave in leads II and III. The dextrose tolerance test showed a sugar content of 68 mg. per hundred cubic centimeters of blood during fasting; one-half hour after the

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1. The preparation used was antuitrin.

ingestion of 100 Gm. of dextrose the value was 116 mg.; in one hour it was 120 mg., and in two hours, 105 mg. Gastric analysis showed free hydrochloric acid after the administration of alcohol and histamine. The erythrocyte count was 2,700,000, and the hemoglobin content, 63 per cent.

The hypophysial preparation was then replaced by 0.064 Gm. of desiccated thyroid three times a day and a diet with a high caloric and high vitamin content. After three months of this treatment the basal metabolic rate was —26 and the temperature 36.6 C. (97 F.); but the weight had fallen to 100 pounds (45.5 Kg.), and the patient had had a few dizzy spells. Thyroid therapy was then discontinued.

In November 1934 the patient's energy was recorded as good, the weight was 117 pounds (53 Kg.) and the temperature was 34 C. (93 F.). In February 1935 she felt "pretty good except for pains in the knees." The weight was 119½ pounds (54 Kg.), and the temperature was 34 C. (93 F.).

Six weeks later, five days before being admitted to the City Hospital, the patient began to vomit and was unable to retain anything until the night before her admission to the hospital, when she took a little orange juice. She was in coma for several hours before being taken to the hospital.

Physical Examination.—The patient was comatose, pallid and covered with perspiration. Breath was slow and shallow. The extremities were cold, and the knees were rigidly flexed but could be forcibly straightened out. No body hair was present. The heart sounds were distant. The temperature was 34.4 C. (94 F.), the pulse rate 84 and the respiratory rate 16. The blood pressure was 140 systolic and 80 diastolic.

Course.—The patient was given 60 cc. of a 50 per cent solution of dextrose intravenously. A generalized convulsion occurred three hours after the patient's admission to the hospital. Respirations stopped but began again after stimulants had been given and artificial respiration had been instituted. The patient died ten hours after her admission to the hospital.

Laboratory Findings.—Analysis of the blood showed: sugar, 21 mg. per hundred cubic centimeters; carbon dioxide, 48.5 volumes per cent; chlorides, 104 mg.; sodium chloride, 172 mg., and urea nitrogen, 6 mg. The urine showed a specific gravity of 1.023, albumin and a few leukocytes.

Clinical Diagnosis.—The diagnosis was hypoglycemia of unknown cause.

Autopsy.—Autopsy was performed four hours after the patient's death by one of us (M. G.). The body was well developed and moderately well nourished, measuring 170 cm. in length and weighing approximately 110 pounds (50 Kg.). The skin and mucous membranes were pale and without any unusual pigmentation or discoloration. There was a conspicuous absence of pubic and axillary hair; the hair on the head was fine, brown and not abundant. The eyebrows and eyelashes were thin. The breasts were small and well developed. A moderate amount of yellow subcutaneous fat was exposed on section. The heart weighed 200 Gm. and showed slight coronary arteriosclerosis. The aorta had a roughened, gelatinous intimal surface and microscopically showed irregular erosion of the intima and swelling and granular degeneration of the fibrous tissue of the intima and media. The lungs showed a small focus of early bronchopneumonia. The liver weighed 850 Gm., and the small lobules were made up of compact parenchymal cells. The spleen weighed 125 Gm. and had a slightly thickened capsule. Histologically a few malpighian bodies were seen to contain secondary nodules of dark brown, pigment-laden phagocytes. The kidneys weighed 75 Gm. each and histologically showed slight arterionephrosclerosis in an unusually compact tissue. The bladder was the seat of slight chronic inflammation.

The hypophysis with attached meninges and dura weighed 0.55 Gm., the weight of the hypophysis alone being estimated as 0.45 Gm. Histologically (fig. 1 *A*) the anterior lobe showed extreme atrophy. The interstitial framework was vaguely present in some situations, and although the acini were almost completely replaced by a granular, filmy, light eosinophilic substance, a rare ill defined cell group could be made out. In the infundibular region was a small area of acinar cells that were better preserved. These cells contained much lipoid in fine to coarse droplets, and with Mallory's stain for connective tissue 97.6 per cent were chromophobic, 0.9 per cent were basophilic and 1.5 per cent were eosinophilic cells. Some of the acini contained colloid, and in the pars intermedia were cystlike spaces filled

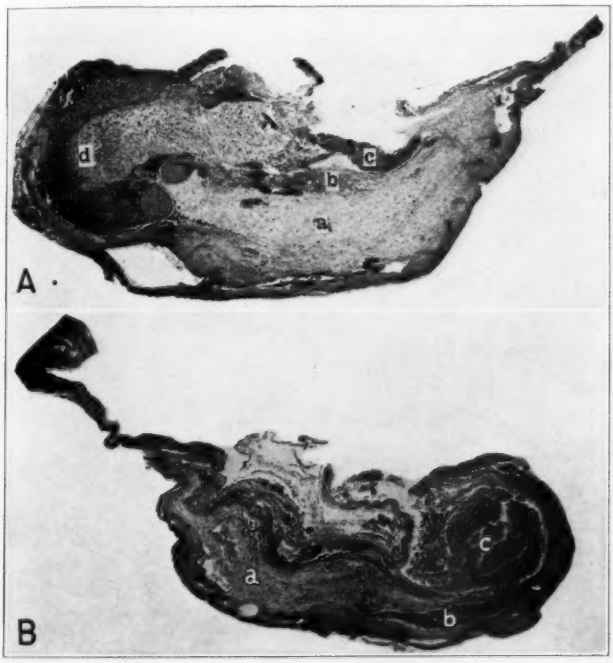

Fig. 1.—The pituitary gland, × 10; hematoxylin and eosin stain. *A*, cross-sections (case 1) showing (*a*) an atrophic fibrotic anterior lobe with (*b*) a zone of hemorrhage and (*c*) a small remaining island of cells of the anterior lobe and (*d*) of the posterior lobe. *B*, cross-section (case 2) showing (*a*) an atrophic fibrotic anterior lobe with (*b*) a narrow band of preserved cells of the anterior lobe and (*c*) of the posterior lobe.

with colloid and lined with cuboidal epithelium. Between the preserved and the atrophic portion of the anterior lobe was an area of hemorrhage in the connective tissue, and brown pigment-laden phagocytes were present in the adjacent fibrous tissue. The posterior lobe showed gliosis which became marked peripherally. The nerve fibers were markedly reduced in number. The entire capsule of the

hypophysis was thickened and fibrous and contained elongated channels lined with flattened epithelium and surrounded by small areas of hemorrhage.

The pineal body weighed 200 mg.; it was yellowish gray, cone shaped and on section finely granular. Histologically, bands of fibrous tissue and neuroglia separated follicular groups of cells which had dark, dense to vesicular nuclei and ill defined eosinophilic cytoplasm, occasionally stippled with basophilic or brown pigment granules. Several corpora arenacea were present.

The thyroid gland weighed 13.5 Gm. and was not grossly fibrous. Histologically (fig. 2*A*) it showed eosinophilic, dense, colloid-filled acini which were unequal in size, generally small and lined with low cuboidal to flat epithelium containing lipoid. There was diffuse interlobular and intralobular fibrosis. There was no conspicuous lymphocytic infiltration. The intralobular capillaries were markedly reduced in number, and the interlobular vessels were surrounded by connective tissue.

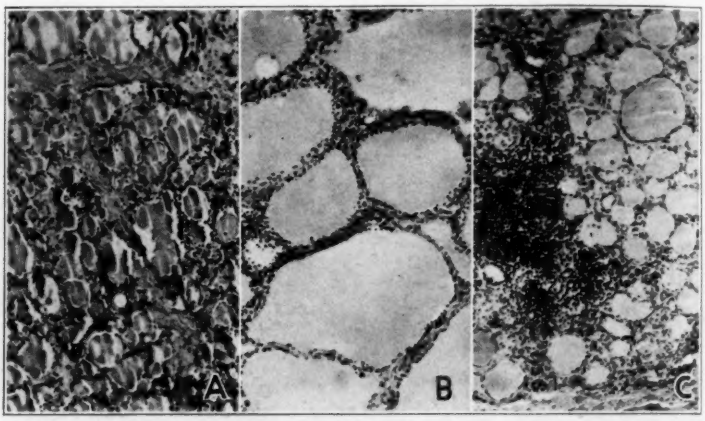

Fig. 2.—Photomicrographs of cross-sections of the thyroid gland; hematoxylin and eosin stain; × 150. *A*, Simmonds' disease (case 1); *B*, acromegaly; *C*, Simmonds' disease (case 2).

Two very small parathyroid glands were present. Histologically (fig. 3*A*) they were composed almost entirely of irregular anastomotic groups of small transitional water-clear cells.[2] In the cytoplasm of these cells was a lipoid-staining area which in some cells was homogeneous and in others granular. This area was about half the size of the nucleus. These groups of cells were separated by similarly disposed, slightly less extensive adipose tissue. A distinct acinar arrangement of slightly larger water-clear cells was present in one small, poorly delimited area. These cells were pyramidal and rested on a distinct basement membrane, with the apexes reaching the center of the lumen. In a rare acinus there was a small amount of colloid. Between these acini was a moderate amount of

2. This is the terminology used by B. Castleman and T. B. Mallory (Am. J. Path. **11**:1, 1935).

connective tissue. One small compact group of pale oxyphilic cells and a few scattered oxyphilic cells were seen. Nonvacuolated principal cells were rare. Small blood sinuses were moderately numerous.

The pancreas weighed 40 Gm. The number of islets per microscopic field was relatively increased. The islets were of average or slightly reduced size and were made up of compact cells that were otherwise normal in appearance. The acinar cells were not unusual. The lobules were small and compact, with moderately prominent, but not thickened, connective tissue septums.

The adrenal glands weighed only 3 Gm. each. On section the cortex was seen to be made up of two rather distinct zones. The outer of these was a semitranslucent yellowish brown tissue; the inner, which measured from 0.5 to 1 mm. in thickness, had the appearance of adrenal cortex. The medulla measured 5 mm. in thickness centrally.

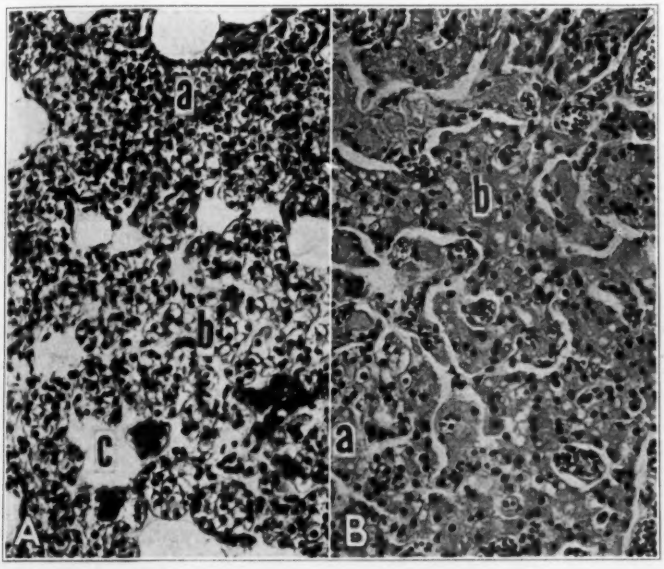

Fig. 3.—Parathyroid glands; hematoxylin and eosin stain; ×250. *A*, Simmonds' disease (case 1), showing (*a*) transitional water-clear cells, (*b*) an adenomatous area of water-clear cells and (*c*) adipose tissue. *B*, acromegaly, showing (*a*) a few transitional water-clear cells and (*b*) transitional oxyphilic cells.

Histologically (fig. 4*A*) the capsule was thickened with dense fibrous tissue, which occasionally enmeshed groups of glomerular zone cells and extended along the interstitial tissue to the medulla. The cortex was markedly narrowed in all zones.

The zona glomerulosa was lacking in many areas, while in others it showed the usual architecture. The small cells contained finely granular, moderately dense eosinophilic cytoplasm with fine lipoid droplets. There were some round, thin nuclei and some smaller, slightly irregularly shaped, dense basophilic nuclei.

The zona fasciculata showed a reduction of the length and number of cells in the individual columns. The cells were polygonal and contained lipoid-filled, faintly eosinophilic staining cytoplasm and round, finely stippled basophilic nuclei. Rarely such columns were grouped together in an adenoma-like area. There were a few narrower columns of dark eosinophilic cells with finely distributed lipoid. Between these two types were intermediate stages, all types containing lipoid, for the most part in large dense globules.

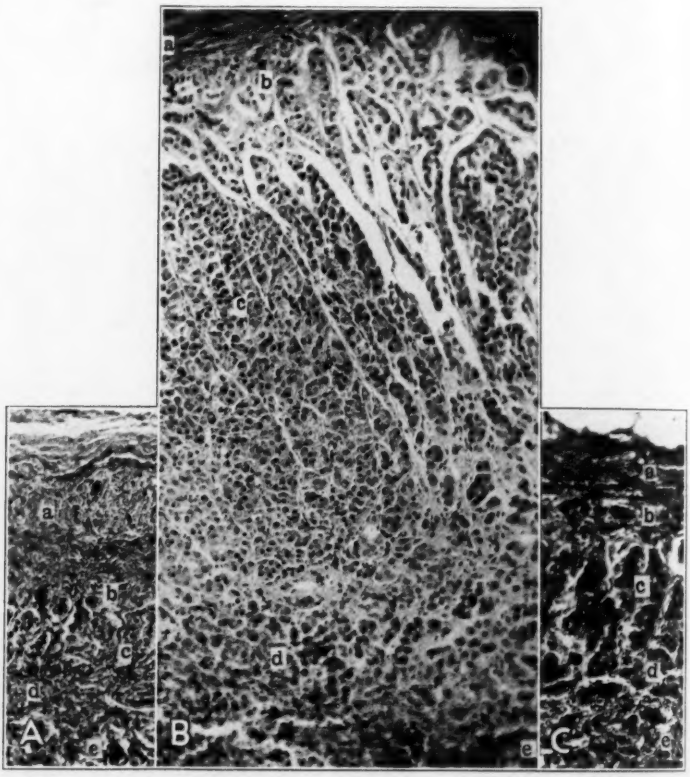

Fig. 4.—Adrenal glands; hematoxylin and eosin stain; × 150. The appearance in Simmonds' disease, case 1 (*A*) and case 2 (*C*), compared with that in acromegaly (*B*). *a* indicates capsule; *b*, zona glomerulosa; *c*, zona fasciculata; *d*, zona reticularis, and, *e*, medulla.

The reticular zone showed a marked increase in fibrous tissue and encapsulated the medulla. The cortical cells scattered in this thickened reticulum had less cytoplasm but were otherwise similar to those first described in the zona fasciculata. Rarely was there a group of compact eosinophilic cells with dense, round basophilic nuclei. A few cells contained fine, light brown pigment.

The medulla showed no fibrosis or apparent atrophy. There was a moderate amount of lipoid in many of the cells.

The uterus weighed 19 Gm. Histologically the endometrium consisted of a single layer of cuboidal cells, with underlying compact fibrous tissue. In the latter tissue were scattered channels lined with cuboidal epithelium. The tubes were cordlike and lined with cuboidal to columnar ciliated epithelium.

The ovaries weighed 1.5 Gm. each. Microscopically they consisted of dense cellular connective tissue without follicles, of corpora albicantia and of thick-walled blood vessels. In the left ovary were a few channels lined with cuboidal epithelium similar to those seen in the uterus.

In the histologic examination of the axillary and pubic skin no apocrine glands were identified. The epithelium was thin, and the papillae were infrequent. The dermis was compact. There were occasional hair follicles, and some were surrounded by compact fibrous dermis. The few sebaceous glands had vacuolated cells and were surrounded by a hyaline capsule. In the subcutaneous tissue were sudoriparous glands and ducts distended with eosinophilic fluid.

The central nervous system was minutely examined. With the Nissl stain, the pia arachnoid showed green granules lying in the cytoplasm of the mesothelial cells and in phagocytic cells lying free in the tissues.

The cerebral cortex showed a diffuse change in the ganglion cells characterized by shrinkage of the cells, with deeply stained triangular or oval nuclei and pale blue homogeneous cytoplasm without Nissl granules or lipoid pigment. The Bielschowsky stain revealed argentophilia of the nuclei of these cells but no fibrillary degeneration or senile plaques. In other cells fine metachromatic granules or deep blue granules appeared to be lying in vacuolated cytoplasm. Cells with pale, swollen nuclei, displaced nucleoli and faintly stained metachromatic cytoplasm appeared in the same field with the cells just described (fig. 6 *A* and *B*). These changes in the ganglion cells were most pronounced in the second, third and fourth cortical layers. The agranular central cortex was the region least affected. Small circumscribed areas of cellular defects (*Verödungsherde*) and diffuse cellular defects were present in many regions (fig. 5).

The fixed glia tissues contained many progressive macroglia cells with large clear nuclei and cytoplasm containing fat-staining green pigment granules. These cells showed no fibril production with the Holzer stain. In some areas of the white matter fat droplets were present in the glia cells. The molecular layer of the cortex contained regressive microglia cells and astrocytes. The capillary walls contained an excessive amount of fat, while the larger blood vessels exhibited perivenous round cell infiltration in many areas (fig. 6 *C*). Periarterial collars of fat filled gitter cells and abundant fat in the adventitia cells were seen, especially in the white matter and the projection pathways. No arteriosclerosis was present. The Nissl stain revealed in the anterior commissure peculiar deep blue homogeneous globules lying along the myelinated fibers.

In other regions besides the cortex changes similar to those described were noted in the ganglion cells but were less extensively distributed. The basal ganglions also contained many astrocytes with fat granules in their cytoplasm. The cerebellum showed only pigment granules in the leptomeninges and the accumulation of products of degeneration around the arteries in the white matter.

Significant changes were observed in the hypothalamus. Serial sections made through this region and compared with similar sections of normal brains revealed a total loss of axis-cylinders in the tuber cinereum coming from the pars nervosa

of the hypophysis.[3] The nucleus supra-opticus showed a marked loss of cells, as compared with the normal condition, and those present exhibited a vacuolar type of degeneration (fig. 6). The supporting tissue consisted of large fibrillary astrocytes and abundant glial fibrosis. No colloid material, such as was described by Scharrer,[4] was present in the cells or supporting tissues. The tract of unmyelinated fibers supposed to connect the nucleus supra-opticus with the pars nervosa of the hypophysis could not be identified in the sections or traced in

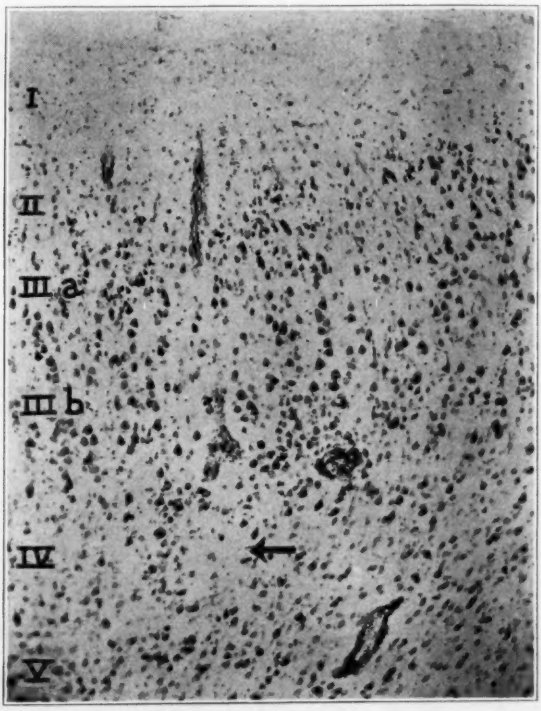

Fig. 5.—The posterior insular region of the cerebral cortex; Nissl stain; × 85. The arrow indicates a small circumscribed cellular defect in lamina IV. Below and to the right is a small vessel with round cell infiltration.

normal material, but the changes seen in the nucleus supra-opticus offered presumptive evidence of such a connection. The number of cells in the nucleus para-

3. Serial sections were made of frozen material in order to obtain more satisfactory Bielschowsky preparations. This entailed considerable technical difficulty.

4. Scharrer, E.: Die Erklärung der scheinbar pathologischen Zellbilder im Nucleus supraopticus und Nucleus paraventricularis, Ztschr. f. d. ges. Neurol. u. Psychiat. **145**:462, 1933.

ventricularis was not reduced, and there was only the type of cellular changes noted in the cortex. No relationship of this nucleus to the pars nervosa of the hypophysis could be identified.

Records of 1 other case in which a diagnosis of Simmonds' disease could be made were found in reviewing the protocols of 7,000 autopsies

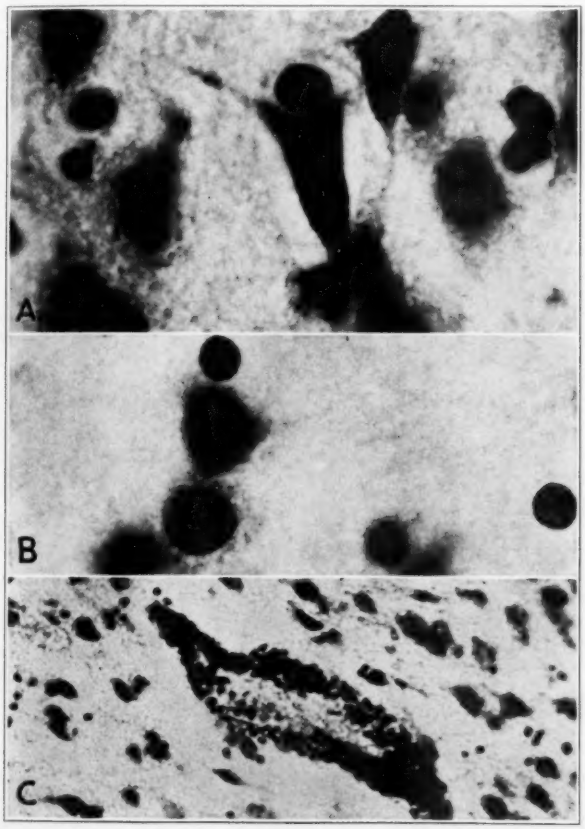

Fig. 6.—*A*, posterior central gyrus; × 2,250. Note the severely shrunken cells with glial satellite. *B*, the parietal region; × 2,250. Note the ganglion cells with a loss of Nissl granules, faintly stained cytoplasm and changes in the nuclei described in the text. *C*, an area of round cell infiltration shown in figure 5; × 300.

at the Cleveland City Hospital and the files of 5,400 autopsies at the Institute of Pathology of the University Hospitals. That case is herewith reported.

CASE 2.—A 60 year old white woman entered the University Hospital on Oct. 5, 1934, in an irrational state. The history was obtained from the daughter.

Clinical History.—The patient was married at the age of 19. She had had one miscarriage and six normal deliveries. When she was 32 years old, toxemia of pregnancy was followed by the menopause. For twelve years she had weekly "sick headaches," urinary frequency and nocturia.

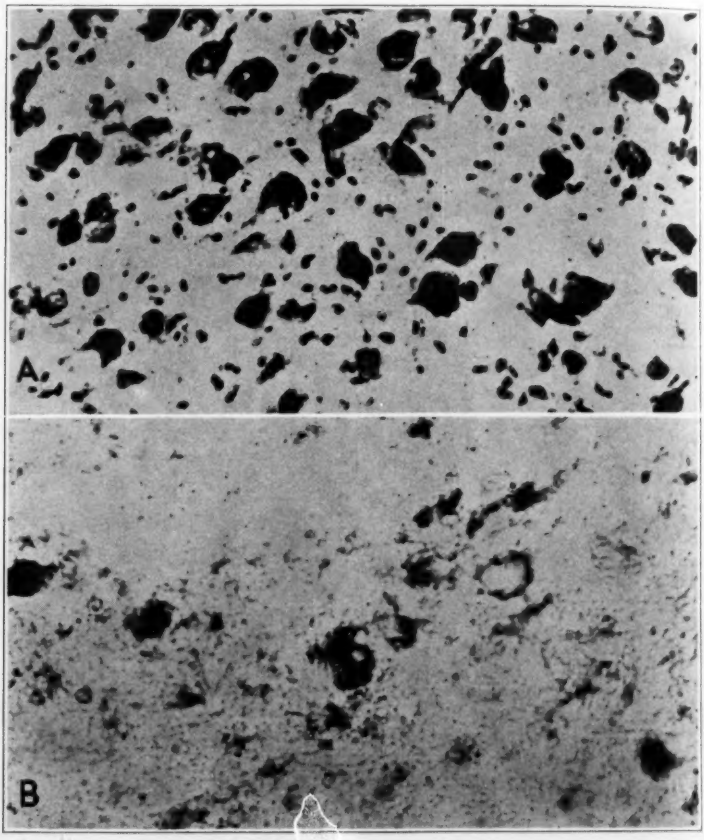

Fig. 7.—Nucleus supra-opticus; Nissl stain; × 300. *A*, normal brain; *B*, Simmonds' disease. Note the loss of ganglion cells, with vacuolation and degeneration of the cells present, and the faintly stained fibrillary astrocytes.

Two years before her admission to the hospital she suddenly had chills and fever and in a few days became irrational. During six weeks of hospitalization at that time these unexplained symptoms gradually subsided. All the teeth were extracted because of severe caries. Similar transient episodes occurred during the next five months. Another attack nine months before her final admission to

the hospital lasted for three weeks and was followed by pains in the knees. These pains had led to incapacitating flexion of the knees for the last seven months.

Two and a half weeks before admission to the hospital the patient showed fatigue, slowness of speech and drowsiness, which in four days progressed to coma with retention of urine. This was followed by an irrational incontinent state without convulsions or paralyses.

Physical Examination.—The patient was an elderly, well developed and fairly well nourished woman. She moaned and cried and was irrational. The skin was fine, soft, dry and pale and vaguely suggested the appearance of brawny edema. The eyebrows and the axillary and pubic hair were scanty. The teeth were absent. The heart was enlarged slightly to the left, and there was a soft systolic murmur over the precordium. The blood pressure was 90 systolic and 55 diastolic. The liver was enlarged, extending 3 fingerbreadths below the costal margin. The legs were not atrophic but were held stiffly in 90 degree flexion, with apparent voluntary contraction of the hamstring muscles. The temperature was 37.8 C. (99 F.). The pulse rate was 70 and the respiratory rate 18.

Laboratory Findings.—The urine was loaded with leukocytes. The blood showed: erythrocytes, 3,500,000; hemoglobin, 83 per cent, and leukocytes, 4,950. The Wassermann test of the blood was negative. The protein content of the plasma was 6.61 Gm., with an albumin-globulin ratio of 1.1. The blood contained 14 mg. of urea nitrogen per hundred cubic centimeters. Gastric analysis showed free hydrochloric acid during fasting. A phenolsulfonphthalein test showed a 5 per cent output during the first hour and a 10 per cent output during the second hour.

Course.—Treatment consisted of inserting an inlying catheter and irrigations of the bladder. The temperature for the first five days was elevated to 39.8 C. (103 F.), after which it fell to between 37 and 37.5 C. (98.6 and 99.5 F.). The slightly myxedematous appearance of the skin and infrequent shallow respirations, even with fever, suggested thyroid deficiency. The basal metabolic rates obtained on the fifth, sixth and seventh days of hospitalization were —16, —36 and —34, respectively. Twice a day 0.032 Gm. of desiccated thyroid was given, the dose being increased to 0.064 Gm. on the tenth day and further increased to three times daily on the sixteenth day. The basal metabolic rates on the twelfth and fourteenth days were —13 and —34, respectively. Electrocardiographic studies showed a levocardiogram. The PR interval was 0.16 second and the QRS interval 0.08 second. The rate was 82, and there was slurring in leads II and III, with a diphasic contour in lead III.

The mental state cleared for a while to the point of rationality. Later the patient became lethargic, irrational and finally comatose. These symptoms were accompanied with a drop in the blood pressure (from 144 systolic and 86 diastolic to 90 systolic and 62 diastolic) and elevation of the pulse rate (from 76 to 120) and temperature (to 40.5 C., or 105 F.), terminating in death.

A study of the blood made on the day of death showed: urea, 23.4 mg.; sugar, 74 mg.; carbon dioxide, 59.4 volumes per cent; leukocytes, 14,600; neutrophils, 57 per cent; lymphocytes, 26 per cent; eosinophils, 10 per cent; basophils, 3 per cent, and monocytes, 4 per cent.

Clinical Diagnosis.—The diagnosis was pyelocystitis, myxedema and toxic psychosis.

Autopsy.—Dr. G. A. Tischer performed the autopsy five hours post mortem. The body was well developed and moderately well nourished. It weighed 50.5 Kg. and measured 157 cm. in length. The skin was of normal consistency and did not feel thickened. The breasts were small; the genitalia were those of an adult

woman. The hair was scanty. The heart weighed 290 Gm. and showed chronic rheumatic disease with mitral stenosis. The aorta showed intimal plaques with calcification. There was pulmonary emphysema. The liver weighed 1,400 Gm. and microscopically showed subacute periportal hepatitis and an advanced degree of arteriolar sclerosis. A gallstone in the ampulla of the gallbladder completely obstructed the cystic duct. The urinary system was the seat of chronic and acute pyelonephritis and cystitis. The kidneys weighed 130 Gm. each. The gastrointestinal tract showed no significant abnormality.

The hypophysis was very small and difficult to recognize. Histologically (fig. 1 *B*) the capsule of the posterior lobe was markedly thickened with fibrous tissue; it was sharply demarcated from the pars nervosa, which was proportionately decreased in size. The anterior lobe was almost completely replaced by thin, loose, moderately acellular connective tissue in which, adjacent to the pars intermedia and extending peripherally along one side, was a bandlike area containing groups of acinar cells. These cells were not sharply delimited and contained much lipoid, chiefly in large globules. Mallory's stain for connective tissue showed 98.1 per cent chromophobes, 1.6 per cent eosinophils and 0.3 per cent basophils. A few acini filled with colloid and lined with low cuboidal epithelium were present in the intermediate zone.

The pineal body measured 9 by 15 mm. The tissue was made up of follicular groups of interneuroglia and neuroglia cells, the latter being more abundant. The stroma in some areas was reticulum-like and contained only a few scattered neuroglia cells. Several corpora arenacea were noted.

The thyroid weighed 17 Gm. and appeared to be poor in colloid. Histologically the follicles varied little in size. They contained a moderate amount of colloid and were lined with flattened epithelium. There was intralobular and perilobular fibrosis, with marked lymphocytic infiltration and several large lymph follicles. There was moderate arterial and arteriolar sclerosis.

The parathyroid tissue included in the section of the thyroid gland showed principal cells and a few groups of oxyphilic and transitional water-clear cells. One moderately large area showed cuboidal principal cells forming acini filled with dense eosinophilic colloid. Adipose tissue was scattered throughout, arteriosclerosis was marked and small capillaries were moderately numerous.

The pancreas weighed 100 Gm., and histologically the islets and acini appeared normal.

The adrenal glands each weighed 4 Gm., and section revealed no gross fibrosis. Histologically the capsule was thickened with fibrous tissue, and all cortical zones were narrowed. The cortical cells were filled with fat in small and large droplets. The zona reticularis contained moderately coarse, brown pigment and showed no extensive fibrosis. The medulla was not appreciably reduced in size and showed the usual cytologic features.

The uterus was small and firm, and the endometrium was atrophic and hemorrhagic. The tubes were cordlike. The ovaries were small and firm. Histologically they showed several small cystic spaces, some lined with flattened epithelium, others with cuboidal epithelium which showed papillary projections into the lumen. A few cysts contained eosinophilic, homogeneous, acellular material. There were several corpora albicantia. There were areas of extensive hemorrhage. The blood vessels were thickened, and a few were calcified.

The brain weighed 1,250 Gm. and showed marked sclerosis of the small arteries. A thorough study by special neuropathologic methods was not made, and the material is no longer available.

COMMENT

The first patient is considered as showing uncomplicated Simmonds' disease.[5] The differential diagnosis has been well discussed in many of the reports, especially those of Calder,[6] Silver [7] and Gunther and Courville.[8]

Cachexia, which is usually but not always associated with Simmonds' disease, was not present. However, there had been an appreciable loss of weight. It is to be noted that after the preparation of anterior lobe of the hypophysis had been replaced by thyroid the weight fell rapidly. After thyroid was discontinued a high caloric diet was forced. To this the subsequent good nutritional state might be attributed, as cachexia has been prevented by a high carbohydrate intake in experimental animals.[9] However, Wahlberg [10] noted that after thyroid was given to emaciated patients the loss of weight increased, but when thyroid was discontinued the weight rose far beyond previous levels. Of the patients reported on who showed either no cachexia at death or a gain in weight before death, those of Bratton and Field [11] and Aitken and Russell [12] had received thyroid; whereas the patients of Hirsch and Berberich [13] and Hantschmann,[14] although they had been given a preparation of the anterior lobe of the hypophysis,[15] received no thyroid. Fahr's [16] patient received no glandular therapy. Tauber's [17] patient

5. Simmonds, M.: Ueber Kachexie hypophysären Ursprungs, Deutsche med. Wchnschr. **42**:190, 1916.

6. Calder, R. M.: Anterior Pituitary Insufficiency (Simmonds' Disease), Bull. Johns Hopkins Hosp. **50**:87 (Feb.) 1932.

7. Silver, S.: Simmonds' Disease (Cachexia Hypophyseopriva): Report of Case with Postmortem Observations and a Review of the Literature, Arch. Int. Med. **51**:175 (Feb.) 1933.

8. Gunther, L., and Courville, C. B.: Hypophyseal Cachexia (Simmonds' Disease) with Atrophy of Anterior Lobe of Pituitary Gland: Report of Case, J. Nerv. & Ment. Dis. **82**:40 (July) 1935.

9. Mahoney, W.: Hypoglycemia Hypophysiopriva, Am. J. Physiol. **109**:475 (Sept.) 1934.

10. Wahlberg, J.: Asthenia Gravis Hypophyseogenea, Acta med. Scandinav. **84**:550, 1935.

11. Bratton, A. B., and Field, A. B.: Case of Simmonds' Disease, Lancet **2**:806 (Oct. 13) 1934.

12. Aitkin, R. S., and Russell, D. S.: Case of Simmonds' Syndrome, Lancet **2**:802 (Oct. 13) 1934.

13. Hirsch, S., and Berberich, J.: Beitrag zur Frage der multiplen Blutdrüsensklerose (pluriglanduläre Insuffizienz), Klin. Wchnschr. **3**:483, 1924.

14. Hantschmann, L.: Beitrag zu den Stoffwechselstörungen bei Hypophysenvorderlappenausfall, Deutsches Arch. f. klin. Med. **176**:397, 1934.

15. The preparation used was praephyson.

16. Fahr, T.: Beitrag zur Pathologie der Hypophyse, Deutsche med. Wchnschr. **44**:206, 1918.

17. Tauber, R. L.: Zur Kenntnis der Simmondsschen Krankheit, Med. Klin. **23**:1499 (Sept. 30) 1927.

died of an intercurrent infection, as did the second patient of this report. The explanation which Wahlberg [18] gave for the gain in weight in cases of functional insufficiency of the anterior lobe in which treatment with thyroid was given does not hold in our case; the hypophysis was atrophic beyond the probability of restoration through the relief of one of its functions over a relatively short period. That hypophysioprivic cachexia is dependent on adrenocortical damage, as suggested by Evans,[19] was not substantiated in this case; the adrenal glands were markedly fibrosed and atrophic, and there was no reason for believing that there was cortical repair during the period in which weight was gained.

The complaint of pain in the joints, which was severe in both the cases here reported, has never been noted as characteristic of Simmonds' disease. It was recorded in the history of each of the patients reported on by Schaefer,[20] Hochstetter,[21] Jakob,[22] Graubner,[23] Fink [24] and Bratton and Field,[11] the ages ranging from 22 to 52 years. The incidence of arthritis in anterior hypophysial insufficiency is, therefore, much lower than that found by Monroe [25] in thyroid insufficiency; this suggests that the arthritis may be associated with the secondary involvement of other ductless glands rather than with primary hypophysial insufficiency.

The favorable response to the active principle of the anterior lobe of the hypophysis, which unfortunately was lost sight of when it was discovered that the basal metabolic rate was low, has been frequently reported recently in cases in which a clinical diagnosis of Simmonds' disease was made. No patient for whom this therapy was considered successful has yet been subjected to postmortem examination. The

18. Wahlberg, J.: Hypophyseothyrogenic Adiposity and Emaciation, J. A. M. A. **106**:1968 (June 6) 1936.

19. Evans, H. M.; Meyer, K.; Pencharz, R. I., and Simpson, M. E.: Cure of Cachexia Following Hypophysectomy by Administration of Growth Hormone and Its Relation to Resulting Adreno-Cortical Repair, Science **75**:442 (April 22) 1932.

20. Schaefer, H.: Beitrag zur Lehre von den Entzündungen specifischer und nicht spezifischer Natur in der Hypophyse, Inaug. Dissert., Pathologisches Institut, Jena, 1919; Centralbl. f. allg. Path. u. path. Anat. **30**:520, 1920.

21. Hochstetter, F.: Beiträge zur Klinik der multiplen Blutdrüsensklerose, Med. Klin. **18**:661 (May 21) 1922.

22. Jakob, A.: Zwei Fälle von Simmondscher Krankheit (hypophysäre Kachexie), Virchows Arch. f. path. Anat. **246**:151, 1923.

23. Graubner, W.: Die hypophysäre Kachexia (Simmondssche Krankheit), Ztschr. f. klin. Med. **101**:249, 1925.

24. Fink, E. B.: Gumma of the Hypophysis and Hypothalamus, Arch. Path. **15**:631 (May) 1933.

25. Monroe, R. T.: Chronic Arthritis in Hyperthyroidism and Myxedema, New England J. Med. **212**:1074 (June 6) 1935.

patients of Simmonds [26] and Hirsch and Berberich [13] showed temporary improvement. A patient with far advanced Simmonds' disease reported on by Weinstein [27] did not respond to pituitary substance, and although the patient reported on by Hantschmann [14] appeared to be improving, death from empyema in a month makes evaluation difficult. As Silver [7] emphasized, there must be a conservative interpretation of the results of substitution therapy in a disease which may have spontaneous remissions and may be of long duration. The 1 cc. of a preparation of anterior lobe of the hypophysis once a week given to the patient here reported on seems theoretically inadequate in view of the extensive atrophy of the anterior lobe of the hypophysis. Although Smith [28] and Evans [19] have shown that in hypophysectomized rats the atrophic endocrine glands are repaired during hypophysial substitution therapy, there are no reports of the effects of such treatment on atrophic ductless glands which show extensive fibrosis. It seems unlikely that adrenal and thyroid glands that were atrophic and stenosed to the extent seen in the case here reported could adequately respond to the active principle of the anterior lobe of the hypophysis. However, experimental and clinical investigations of this fundamental problem are necessary before any conclusions can be drawn and a rational therapy for Simmonds' disease established.

Extensive studies of the chemical changes in the blood in the episodic or terminal coma of Simmonds' disease have never been reported. Studies such as those made by Loeb [29] in adrenal insufficiency would be of great interest. In several cases determinations of the sugar content of the blood have been made, and there was marked hypoglycemia, as was present in our case 1. The extremely low content of chloride in the blood, which unfortunately there was no opportunity to check, is of interest because of the atrophic condition of the adrenal glands, but there was no corresponding hypotension, the blood pressure at the time being 114 systolic and 80 diastolic.

The interesting postmortem observations in this case, aside from those generally reported in Simmonds' disease, were neuropathologic and confirmed those of Jakob,[22] who emphasized the importance of changes in the nervous system in Simmonds' disease. The diffuse uncharacteristic changes in the ganglion cells, unassociated with the presence of

26. Simmonds, M.: Atrophie des Hypophysenvorderlappens und hypophysäre Kachexie, Deutsche med. Wchnschr. **44**:852, 1918.

27. Weinstein, A.: Multiglandular Syndromes Resembling Simmonds' Discase, with Case Report, Am. J. M. Sc. **189**:245 (Feb.) 1935.

28. Smith, P. E.: Hypophysectomy and Replacement Therapy in the Rat, Am. J. Anat. **45**:205 (March 30) 1930.

29. Loeb, R. F.: Chemical Changes in the Blood in Addison's Disease, Science **76**:420 (Nov. 4) 1932.

excessive lipoid pigment or fatty sclerosis, the areas of cellular defects, the protoplasmic growth of the glia cells and the absence of senile plaques and fibrillary degeneration of the nerve cells are identical with his observations. The involvement of the inferior olive, the dentate nucleus of the cerebellum and the corpuscular bodies described by Jakob was not seen. Degenerative products and round cell infiltration around the blood vessels were not noted in Jakob's case but are frequently seen in senile dementia. Otherwise the changes were not similar to those of the senile involutionary process, although definitely of a retrograde or degenerative character. The round cell infiltration represented "symptomatic inflammation" (Spielmeyer) and is not considered an indication of encephalitis. Jakob's observations, which we have confirmed, have apparently not been described by other observers. The changes probably depend on the metabolic disturbances secondary to polyglandular insufficiency and may contribute to the mental symptoms of Simmonds' disease. Jakob observed in a patient with Addison's disease changes like those he described in Simmonds' disease.

In an attempt to determine the significant anatomic changes in the ductless glands in this case of pluriglandular insufficiency, the case was studied in conjunction with one of pluriglandular hyperfunction. The latter was a typical case of acromegaly in a 39 year old man who came to autopsy with a picture in general similar to that reported by Cushing and Davidoff.[30] The conspicuous difference between Simmonds' disease and acromegaly, apart from size, is the vascularity of the ductless glands. In acromegaly there are numerous thin-walled capillaries adjacent to the glandular units, whereas in Simmonds' disease the capillaries, markedly decreased in number, are usually surrounded by interstitial fibrous tissue. In the thyroid gland (fig. 2) the colloid in Simmonds' disease is dense, that in acromegaly is thin and pale; the lining cells of the acini are more cuboidal and contain less fat in acromegaly and there is relatively no fibrous interstitial tissue. The parathyroid glands in acromegaly (fig. 3) contain no interstitial adipose tissue and are composed of medium-sized principal cells which border on the pale oxyphilic type, contain little or no lipoid and are arranged in columns, frequently adjacent to large sinusoids containing a thin eosinophilic edema-like substance and capillaries. In neither case is there an appreciable number of definite oxyphilic cells. The parathyroid gland in Simmonds' disease is similar to that described by Jakob [22] in his case but does not correspond in detail to the type described by Houssay [31] after hypophysectomy in animals;

30. Cushing, H., and Davidoff, L. M.: The Pathological Findings in Four Autopsied Cases of Acromegaly, with a Discussion of Their Significance, Monograph 22, Rockefeller Institute for Medical Research, April 23, 1927.

31. Houssay, B. A.: Certain Relations Between the Parathyroid, the Hypophysis and the Pancreas, New England J. Med. **214**:1128 (June 4) 1936.

not does the parathyroid gland in acromegaly have the same structure as that briefly described by him in induced hyperpituitarism in animals. In routine sections of the pancreas stained with hematoxylin and eosin and with stains for fat, the islets of Langerhans appear to be made up of similar cells, which in acromegaly have slightly more cytoplasm but are not more numerous. The fibrosis noted in other glands in Simmonds' disease is not present in the pancreas. In the adrenal glands there is a great difference (fig. 4). The zona reticularis in Simmonds' disease (our case 1) is fibrous, and only a rare shrunken pigmented cell remains; this contrasts markedly with the wide zona reticularis in the case of acromegaly in which the cells were large and laden with pigment. The lipoid, which is extensively deposited throughout the adrenal gland in Simmonds' disease, is present chiefly in the zona glomerulosa and in the peripheral third of the zona fasciculata in the adrenal gland in acromegaly. Although the adrenal glands in this particular case of Simmonds' disease did not correspond to any of the types described by Zwemer,[32] those of the acromegalic patient corresponded in most respects to his type of "severe exhaustion of the adrenal."

The second patient here reported on may be classed as having Simmonds' disease but dying of intercurrent infection; the history and symptoms were those of both conditions, and the effect of this interrelationship is difficult to evaluate. Periods of fever and mental disturbances have been previously reported in Simmonds' disease.[27] Whether cachexia and microsplanchnia would have developed had the patient not succumbed to an intercurrent infection is impossible to determine. The only anatomic feature by which the diagnosis of Simmonds' disease may be justified is atrophy of the pituitary out of proportion to the general glandular atrophy.

SUMMARY

Two patients with Simmonds' disease are reported on. The first patient showed the typical postmortem picture of fibrosis and almost complete atrophy of the anterior lobe of the hypophysis, fibrosis and marked atrophy of the adrenal glands, thyroid glands and gonads, as well as visceral microsplanchnia. The patient showed the characteristic history of onset following a complicated pregnancy and the loss of hair, teeth and sexual functions, and symptoms of weakness, chilliness and poor appetite, together with a subnormal temperature, a low basal metabolic rate, an increased sugar tolerance and anemia and a fatal termination in hypoglycemic coma. The lack of cachexia was explained as a result possibly of therapy. The central nervous system showed an uncharacteristic diffuse disease of the ganglion and glia cells and cellular

32. Zwemer, R. L.: Study of Adrenal Cortex Morphology, Am. J. Path. **12**: 107 (Jan.) 1936.

defects in the cortex, changes which confirmed the observations of Jakob. The nucleus supra-opticus exhibited loss and degeneration of the ganglion cells.

The second patient presented several characteristics of Simmonds' disease—the onset of the menopause following toxemia of pregnancy, fatigue, mental disturbances, scanty body hair, a low basal metabolic rate and at autopsy an almost completely atrophic anterior lobe of the hypophysis and moderately atrophic adrenal and thyroid glands; but cachexia had never developed, death was not in hypoglycemic coma and there was no visceral microsplanchnia. The additional history of episodes of chills and fever and the finding of chronic and acute cystitis and pyelonephritis suggested that this intercurrent infection rather than Simmonds' disease was the terminating factor.

In both cases pain in the knees was a prominent symptom.

A REVIEW OF FOUR HUNDRED AND FORTY CASES OF PELLAGRA

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From a clinical standpoint the problems of the etiology and treatment of pellagra remain unsolved, and the mortality rates in general hospitals range between 20 and 50 per cent. In an effort to determine the most promising fields for further inquiry into the etiology of pellagra and also to determine the causes of such persistently high death rates, the records of 440 patients with this disease were analyzed. When patients were admitted to the hospital more than once, the new data were added to those previously recorded; no patient was counted twice. The interval over which the observations were made covered the sixteen years between Jan. 1, 1919, and Dec. 31, 1934.

Several reviews of pellagra have appeared during recent years, notably those of Turner,[1] Boggs and Padget,[2] Mulholland and King [3] and Garrett.[4] It was felt that our series, being considerably larger than those previously reviewed and representing patients drawn from a relatively small community which has perhaps undergone less economic stress during the past decade than larger centers of population, might throw added light on the problem.

The diagnosis was based on the usual criteria of stomatitis with glossitis, dermatitis of characteristic type, diarrhea and psychoses. The diagnosis was not considered established unless at least two of these conditions were present. In many instances typical glossitis and dermatitis were considered adequate.

As shown in chart 1, there was a marked increase in pellagra after 1924, the peak being reached in 1929, with sharp declines in 1930

From the University of Georgia School of Medicine, and the University Hospital.

1. Turner, R. H.: Pathologic Physiology of Pellagra: Tabulated Clinical and Physiological Data, J. Clin. Investigation **10**:61-70 (April) 1931.

2. Boggs, T. R., and Padget, P.: Pellagra: Analysis of One Hundred and Two Cases, Bull. Johns Hopkins Hosp. **50**:21-32 (Jan.) 1932.

3. Mulholland, H. B., and King, R. L.: Pellagra: Review of Cases with Special Reference to Gastric Secretions, J. A. M. A. **101**:576-580 (Aug. 19) 1933.

4. Garrett, T. C.: Analysis of Cases of Pellagra Admitted to Pennsylvania Hospital Since 1922, Am. J. M. Sc. **190**:525-535 (Oct.) 1935.

and 1934. No adequate explanation has been offered for the increase in 1929. This was a period of relative prosperity and great industrial activity in the community, few persons were unemployed and the general scale of living was perhaps at an all time high level in all classes of the population. Alcoholism was not a factor.

Chart 2 shows the incidence of pellagra by months. There was the usual seasonal distribution, the greatest number of patients being admitted during the early summer. As the average duration of symptoms prior to hospitalization was four weeks, the July peak therefore represented cases beginning in May and June. However, pellagra occurred throughout the year.

Of the 440 patients, 250 were white patients and 190 were Negroes, all from a population almost exactly divided between the races. Of the white patients, 88 (35.2 per cent) were males and 162 (64.8 per

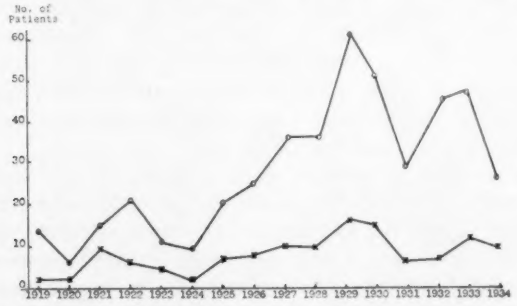

Chart 1.—The incidence (upper line) and the mortality (lower line) of pellagra.

cent) were females. Of the Negroes, 56 (29.5 per cent) were males and 134 (70.5 per cent) were females.

The age distribution was wide, patients of all ages between 5 and 89 years being observed. The ages of over half (285) fell into the three decades between 21 and 50 years, inclusive.

The death rate showed differences, possibly of significance, as to race and sex. Of the white males, 22 (25 per cent) died; of the white females, 33 (20.4 per cent) died. The total mortality among the white patients was 22.7 per cent. Of the Negroes, 28.5 per cent of the males and 35.8 per cent of the females did not recover. The total mortality among Negroes was 33.7 per cent (chart 3). The effect of yeast therapy was probably reflected in the death rate. During the seven years between 1919 and 1925 92 patients were treated with a high protein, high caloric diet, with the addition of citrus fruit juice, milk, cod liver oil and diluted hydrochloric acid. Many were fed by tube to insure adequate nourishment, and a large number were given arsenic in various

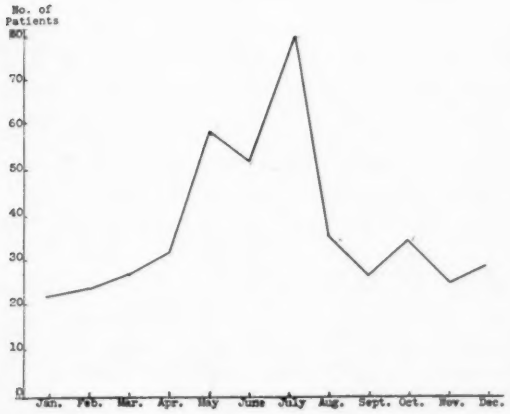

Chart 2.—The incidence of pellagra by months.

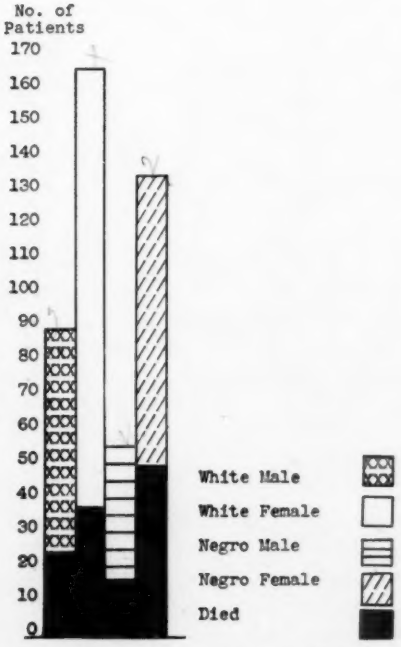

Chart 3.—The incidence and mortality rate of pellagra by race and sex.

forms. This group of patients showed a 33.7 per cent mortality. During January 1926, at Dr. Goldberger's suggestion, dried yeast was added to the diet in amounts varying between 30 and 90 Gm. daily, and all empirical medication was discontinued. During the ensuing nine years 348 patients were treated, 88 (25.3 per cent) of whom died; the favorable differential under yeast treatment was therefore 8.4 per cent. The total percentage of deaths during the entire period was 27.04 per cent. The largest number of deaths occurred among patients in the age group from 31 to 50, and the actual rate of mortality increased sharply after the fourth decade (chart 4).

The occurrence of "cardinal" symptoms and signs and their apparent relation to the fatal outcomes is shown in table 1. No very significant differences were present, except in the incidence of psychoses; these were noted nearly twice as frequently in the fatal cases.

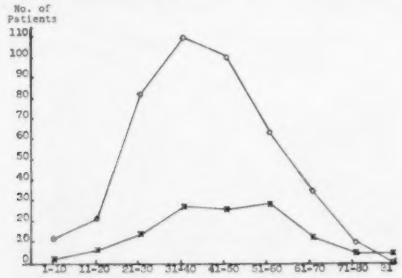

Chart 4.—The age incidence (indicated by o's) and the mortality rate (indicated by x's) by decades.

The incidence of fever was studied on account of the widely held opinion that a persistent or marked elevation of temperature without definite infection carries a bad prognosis. Complications which were considered adequate cause for fever occurred in 68 patients (table 4); among the remainder of the group temperatures exceeding 99.5 F. were recorded over periods of not less than five days in 222 instances. High fever was seen almost exclusively among those who died. The relative distribution of pyrexia is shown in table 2.

Considerable importance was attached to examinations of the blood. Estimations of the sugar and nonprotein nitrogen contents of the blood were made 420 times, and nothing of significance was observed. Hemoglobin determinations by Sahli's method and erythrocyte and leukocyte counts were obtained for all but a few patients. Anemia was considered present when the hemoglobin value was below 80 per cent and the red cell count below 4,000,000. In certain instances anemia was certainly masked by dehydration, usually in the most severely ill patients,

for many of whom only one examination of the blood was made. Anemia was present in 83.6 per cent of the patients; in 22 patients (5 per cent) the color index exceeded 1.1, and the anemia was classed

TABLE 1.—*Distribution of Cardinal Signs and Symptoms*

	Patients Who Recovered (321)	Percentage	Patients Who Died (119)	Percentage	Total Number of Patients	Percentage of Entire Group
Glossitis and stomatitis	310	96.5	117	98.3	427	97.04
Dermatitis	299	93.1	117	98.3	416	94.50
Diarrhea	220	68.5	91	76.5	311	70.70
Psychoses	130	40.5	91	76.5	221	50.20

TABLE 2.—*Range of Temperature*

	Temperature, F.				
	99.6-101	101-102	102-103	103-106	Total
Patients who recovered	86	15	8	3	112
Patients who died	36	14	10	50	110
Totals	122	29	18	53	222

TABLE 3.—*Results of Examinations of the Blood*

	Hemoglobin, %							
	20-29	30-39	40-49	50-59	60-69	70-79	80-95	Total
Patients who recovered	3	3	20	42	84	110	57	319
Patients who died	3	6	11	22	21	33	18	114
Totals	6	9	31	64	105	143	75	433

	Erythrocytes, Millions							
	1-1.4	1.5-1.9	2-2.4	2.5-2.9	3-3.4	3.5-3.9	4-4.8	Total
Patients who recovered	1	1	12	29	66	78	134	321
Patients who died	1	4	9	10	21	22	41	118
Totals	2	5	21	39	87	100	175	439

	Leukocytes, Thousands					
	Below 5	5-7.4	7.5-9.9	10-12.4	12.5-18	Total
Patients who recovered	29	96	121	48	24	318
Patients who died	12	40	27	10	24	113
Totals	41	136	148	58	48	431

as hyperchromic (unfortunately, the volume index was not determined for these patients). The remaining 77.6 per cent of the group definitely showed hypochromic anemia. The leukocyte counts were of no special significance, counts above 7,400 being recorded 254 times. The degree and distribution of anemia and of leukopenia and leukocytosis are shown in table 3.

The gastric content in its relation to adequate gastric function is a matter of much interest and possible importance. In this series only 247 patients had test meals, as the importance of this procedure was not appreciated during the earlier years. The Ewald meal was used, and in most instances the fractional method of withdrawal was practiced; histamine was not used. It was noted that the amount of the contents recovered after a test meal was almost uniformly small, seldom exceeding 50 cc. In patients with apparent anacidity the late appearance of

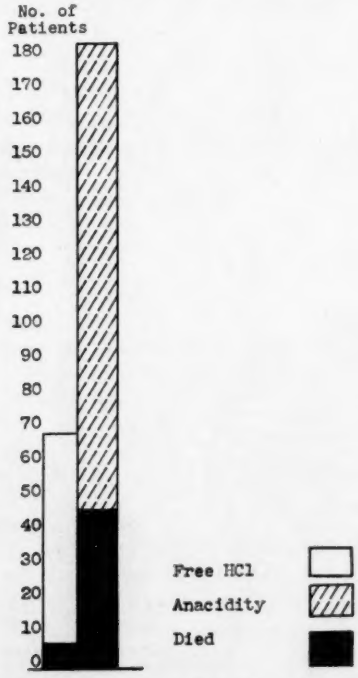

Chart 5.—The relation between gastric acidity and the mortality rate.

free acid was not noted. In 67 patients there was some free hydrochloric acid; 6 of these patients died, giving a mortality rate of 8.9 per cent. Achlorhydria was shown by 180, 43 (23.9 per cent) of whom did not recover. Seventy (36.3 per cent) of the 193 patients whose gastric content was not examined succumbed. The apparent relation of achlorhydria to the mortality rate is shown in chart 5.

Neurologic disturbances other than psychoses were not frequent, and in this respect our series varied widely from those reported by others.

Some evidences of combined sclerosis were noted in 33 patients (7.5 per cent) and peripheral neuritis in only 11 patients (2.5 per cent). The very low incidence of peripheral neuritis may possibly be accounted for by the relative rarity of alcoholism among our patients.

Alcohol as a causative or precipitating factor of pellagra had no influence comparable to that noted in the experience of Boggs and

TABLE 4.—*Complications*

Disease	Number of Patients	Patients Who Recovered	Patients Who Died
Amebiasis	3	3	0
Arteriosclerosis	10	8	2
Arthritis, chronic	2	1	1
Asthma	3	3	0
Bronchopneumonia	25	2	23
Cerebral hemorrhage	2	1	1
Granuloma venereum	2	2	0
Heart disease (all types)	30	22	8
Helminthiasis	5	5	0
Hypertension (essential)	7	5	2
Hyperthyroidism	1	1	0
Malaria	4	4	0
Meningitis (septic)	1	0	1
Morphinism	2	2	0
Nephritis (all types)	4	1	3
Obesity	1	1	0
Otitis media, acute	1	0	1
Pelvic inflammation	14	11	3
Pneumonia, lobar	2	0	2
Pulmonary abscess	1	0	1
Starvation	4	0	4
Syphilis (all stages)	57	42	15
Tuberculosis	18	12	6
Urinary infections	13	13	0

TABLE 5.—*Relation of Recovery to Extent of Hospitalization*

Days in Hospital	Patients Who Recovered	Patients Who Died
1- 7	24	54
8-14	73	34
15-21	86	13
22-28	39	5
29-35	31	2
36-42	22	5
43-49	14	2
50-56	5	2
57-63	9	0
64 and over	18	2

Padget [2] or of Spies and DeWolf.[5] A history of severe acute or chronic alcoholism was obtained for only 38 patients (8.8 per cent). In practically every instance it was felt that it did have a direct bearing on the development of pellagra. In the great majority there had been a tremendous consumption of unaged illicitly distilled corn whisky over a relatively short period, varying from two to eight weeks prior to the

5. Spies, T. D., and DeWolf, H. F.: Observations on the Etiologic Relationship of Severe Alcoholism to Pellagra, Am. J. M. Sc. **186**:521-525 (Oct.) 1933.

onset of symptoms. The occurrence of peripheral neuritis was much more frequent in the group of alcoholic patients (8 of the 11 instances). The mortality rate was not influenced by alcohol—8 of the 38 alcoholic patients died.

Complications were recognized in 215 patients, and their nature and relation to the mortality are shown in table 4. Severe acute pulmonary infection, heart disease and possibly syphilis were the only concurrent ailments which seemed to have a definite influence on the outcome.

As a matter of interest the relation of recovery to the duration of hospitalization was noted. It is significant that 45.4 per cent of the deaths occurred during the first week of hospitalization and 73.7 per cent during the first two weeks. These patients showed an advanced, dehydrated and usually febrile condition and were profoundly demented, not being amenable to any form of therapy yet suggested. The data are presented in table 5.

COMMENT AND CONCLUSIONS

The items of possible significance which appear in this analysis are few but rather well defined. The relatively high death rate among Negroes is difficult of explanation. Syphilis and tuberculosis are more common among them than among white persons, but these diseases do not account for more than a small fraction of the difference in mortality. Contrary to the general impression, the southern Negro lives well; and while his diet may be somewhat low in proteins of optimum biologic value, it is rich in green vegetables of good vitamin B_2 content. Neglect of symptoms cannot be considered the cause, as the Negro population from which these patients were drawn has been the object of almost paternal medical supervision for about a century, and medical advice is sought by them for the most trivial complaints.

The incidence of lesions of the spinal cord and of peripheral neuritis was notably less among our patients than that noted in other reports; on the other hand, psychoses attributable to pellagra were considerably more frequent. It is possible that these conditions depend on the factors precipitating the syndrome. When alcoholism is important, lesions of the peripheral nerves seem to be much more frequent.

Alcohol as an apparent etiologic factor was almost negligible in this group, but that it may be a potent cause of pellagra is not denied. It is well known that the gastric function is greatly impaired by severe alcoholism, and this we believe to be of greater importance than any inadequate intake of food during a spree.

Anemia occurred frequently, but in the great majority of patients it was definitely hypochromic. A few patients who showed a color index greater than unity were not controlled by determinations of the volume index. Studies of the bone marrow of a small number of patients

with severe pellagra indicated that its reaction is definitely nonspecific.[6] These observations are in accord with those of other authors.

The importance of gastric dysfunction and possibly of hepatic changes has not been generally emphasized. Mulholland and King [3] discounted it, Boggs and Padget [2] and Spies and Payne [7] have stressed it. We have been particularly impressed by the frequency of anacidity and by the inadequate amounts of gastric contents recovered from pellagrins even when free hydrochloric acid was present. Helmer, Fouts and Zerfas [8] have shown that the pepsin and rennin contents are diminished in the gastric mucosa of patients with pellagra. That a grave defect of gastric function exists seems most likely, and experiments carried out in this clinic suggest that it is the determining factor in the production of the syndrome.[9] Lesions of the liver, most often fatty degeneration, are present in a great majority of the patients coming to necropsy (92 per cent of our small series). These have been noted by all observers, but their significance has been discounted. It seems likely that they may have great importance as part of a picture of gastro-intestinal failure. Levin [10] has expressed the opinion that the liver controls the acid production of the stomach. That the changes in the gastro-intestinal function are primary and causative rather than secondary to pellagra is an attractive hypothesis. Further, it seems probable that these changes result in an intrinsic deficiency analogous to but probably distinct from that which is present in pernicious anemia.

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6. Krjukoff, A.: Blut und Blutbildung bei schweren Fällen von Pellagra, Folia haemat. **45**:196-206 (Sept.) 1931. Vryonis, G. P.: Unpublished observations.

7. Spies, T. D., and Payne, W.: A Study of the Etiologic Relationship Between Pellagra and Pernicious Anemia, J. Clin. Investigation **12**:229-234 (Jan.) 1934.

8. Helmer, O. M.; Fouts, P. J., and Zerfas, L. G.: Gastro-Intestinal Studies: III. Determinations of Enzymes on Autopsy Specimens from Cases of Pernicious Anemia and Pellagra, Arch. Int. Med. **53**:675-679 (May) 1934.

9. Sydenstricker, V. P.; Armstrong, E. S.; Derrick, C. J., and Kemp, P. S.: On the Existence of an Intrinsic Deficiency in Pellagra, Am. J. M. Sc. **192**:1-8, (July) 1936. Sydenstricker, V. P., and Kemp, P. S.: Unpublished observations.

10. Levin, A. L., in discussion on Mulholland and King.[3]

Progress in Internal Medicine

DISEASES OF THE HEART

A REVIEW OF SOME CONTRIBUTIONS MADE DURING 1936

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WITH THE EDITORIAL ASSISTANCE OF
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BOSTON

The suggestion that foreign medical reports be given greater emphasis than heretofore seems worth while, because of the fact that they are less readily available to the average reader. Accordingly, the review this year assumes a more international character. The material has again been organized very simply, with the etiologic subdivisions made as complete as possible. For example, under the heading "Rheumatic Heart Disease" will be found nearly all the material specifically relating to this illness. No attempt has been made to review the various textbooks and monographs, as this has already been done adequately.

PHYSIOLOGY AND EXPERIMENTAL PATHOLOGY

Investigation of the action of the vagus and sympathetic nerves or of their chemical mediators on the heart is being vigorously pushed.[1]

In an effort better to understand the factors controlling cardiac acceleration during muscular exercise, Brouha, Cannon and Dill[1a] made a series of extremely interesting experiments on totally sympathectomized dogs. Before sympathectomy the average heart rate during rest is around 110 beats a minute; after an emotional stimulus the heart rate may jump to from 180 to 220; during light exercise the rate ranges from 170 to 200; during average exercise the rate stabilizes around 220 to 240; during intense exercise the rate often reaches 240 to 260 in the first six seconds, and, as exercise is prolonged, it

From the Cardiac Clinic of the Massachusetts General Hospital.

1. (*a*) Brouha, L.; Cannon, W. B., and Dill, D. B.: The Heart Rate of the Sympathectomized Dog in Rest and Exercise, J. Physiol. **87**:345, 1936. (*b*) Pinkston, J. O.; Partington, P. F., and Rosenblueth, A.: A Further Study of Reflex Changes of Blood Pressure in Completely Sympathectomized Animals, Am. J. Physiol. **115**:711, 1936. (*c*) Gremels, Hans: Ueber die Steuerung der energetischen Vorgänge am Säugetierherzen, Arch. f. exper. Path. u. Pharmakol. **182**:1, 1936. (*d*) Bronk, D. W.; Ferguson, L. K.; Margaria, R., and Solandt, D. Y.: The Acidity of the Cardiac Sympathetic Centers, Am. J. Physiol. **117**:237, 1936.

may reach 300 to 315. The cardiac deceleration following exercise is not always the same after comparable amounts of exercise, although it drops markedly within six seconds after average or intense exercise.

After total sympathectomy the heart rate averages around 82 beats a minute, which is definitely below that for normal dogs. Respiratory arrhythmia is always more marked than normal. An emotional stimulus always produces cardiac acceleration, and the rate may jump from 80 to 140 or even 180 beats a minute; during light exercise it stabilizes between 120 and 140 and during average exercise between 160 and 200; during intense exercise following a sudden initial acceleration there is a progressive rise to 200 or more. Cardiac deceleration follows the normal pattern.

Three months after operation the heart rate remains slow, but the capacity for work is about normal; exercise is accomplished without effort; muscular coordination is faultless, and the animals are not short of breath and show normal fatigability. The sugar and lactic acid content of the blood, the alkali reserve and the body temperature vary within normal limits.

The explanation of this cardiac acceleration in totally sympathectomized dogs, which is only 30 or 40 per cent below normal, was not found in a change of body temperature, the action of muscular metabolites or the liberation of epinephrine or sympathin. They did find that when atropine was injected the heart rate reached from 210 to 230 beats a minute. The same dose of atropine after section of both vagus nerves produced no effect, the rate stabilizing around 130 beats a minute; but stimulation of the peripheral ends of both vagus nerves resulted in cardiac acceleration, which in one dog reached 230 beats a minute. The authors concluded from this that bilateral vagotomy suppresses some accelerator mechanism which comes into play during exercise or under the influence of atropine. This mechanism is not seen in cats, but it is probably present in man. The important researches of Jourdan and Nowak are mentioned, wherein they demonstrated in dogs the existence of cardio-accelerator fibers coming from the mesencephalon, leaving the brain by way of the vagus nerve and going down to the vagosympathetic trunk. The same authors have shown that these fibers are put into action during asphyxia.

Anrep, Barsoum and Talaat [2] have shown that the cardiac muscle in the heart-lung preparation of a dog continuously produces measurable quantities of a histamine-like substance. The behavior of this substance in the presence of various chemical reagents and the manner in which

2. Anrep, G. V.; Barsoum, G. S., and Talaat, M.: Liberation of Histamine by the Heart Muscle, J. Physiol. **86**:431, 1936.

it acts on various biologic test objects provide strong evidence that this substance is actually histamine. The production of histamine is increased by raising the blood pressure and to a much greater extent by the administration of epinephrine. In every instance of increased production of histamine there is also an increase of its concentration in the blood of the coronary veins, which suggests the possibility that histamine may participate in the augmentation of coronary blood flow observed when the arterial blood pressure is raised. The important question is raised as to whether the epinephrine acts as a coronary vasodilator by direct action on the sympathetic nerve endings or through the liberation of a metabolite, possibly histamine. Further experimentation is necessary to decide this question. The observation that an excess of carbon dioxide and especially a deficiency in oxygen also cause a conspicuous increase in the production of histamine suggests that this increase may be indirectly due to relative anoxemia or a change in the acid-base equilibrium within the contracting muscle cell.

Radnai and Ascher [3] have made an interesting contribution concerning the compensatory increase in the size of the cardiac valves. The study was actually begun by Radnai in 1929 with the development of a method accurately to determine the surface area of cardiac valves. In the course of his early investigations it appeared that in those cases of syphilitic aortitis and to a lesser degree in arteriosclerosis in which the process was not extended over the aortic valve, this valve was considerably enlarged. Furthermore, it appeared that this valvular enlargement was often of a higher degree than the enlargement of the aortic opening. In certain instances the valve could completely close an aortic opening twice or more than twice normal size. Consequently, relative aortic insufficiency is found uncommonly not because of "rigidity" of the aortic opening but because the dilated opening can be closed by the enlarged healthy aortic valve.

It was only natural to extend this study to the investigation of other cardiac valves. Radnai and Ascher showed that in normal subjects the area of the pulmonary valve is slightly larger than that of the aortic valve. In instances of pulmonary hypertension the pulmonary valve is strikingly enlarged not only in relation to the normal but also in comparison with the normal aortic valve of the same subject. The increase in size of the pulmonary valve stands in close relationship to the degree of hypertrophy of the right ventricle and is similar in degree whether the increase in blood pressure in the pulmonary artery is due to mitral stenosis or to severe emphysema. Enlargement of the

3. Radnai, P., and Ascher, F.: Ueber die kompensierende Vergrösserung der Herzklappen, Deutsches Arch. f. klin. Med. **179**:142, 1936.

pulmonary valve contrasts with that of the aortic valve in that there is a smaller difference between the area of the valve and the size of the opening. Thus there is not the far-reaching protection against the development of relative insufficiency of the pulmonary valve that there is against aortic insufficiency. This discrepancy between the enlargement of the pulmonary and that of the aortic valve is shown in all probability to be due to the different forces at work. In the case of the former, the chief factor is the increase in blood pressure, while in the latter case the chief factor lies in the disease of the aortic wall, which permits the downward displacement of the sinus of Valsalva.

Radnai and Ascher next considered whether this mechanism of compensatory enlargement applies to the mitral valve. The accompanying tabulation summarizes their results:

	Average Value, Sq. Mm.	Maximal Value, Sq. Mm.	Minimal Value, Sq. Mm.
Area of mitral valve in normal subjects	1,573	2,170	1,000
Area of mitral valve in subjects with hypertrophy of left ventricle	1,850	3,000	1,100

The probable mechanism of enlargement of the mitral valve is considered. Because this enlargement is relatively slight, compared with the dilatation of the mitral orifice in instances of hypertrophy of the left ventricle, mitral insufficiency is of common occurrence.

Dieckhoff [4] has pointed out that it has long been known that the hypertrophied heart of a patient in congestive failure is more sensitive to digitalis than is a normal heart. Corresponding experiments on animals have confirmed this observation, and Dieckhoff decided to determine whether the presence of hypertrophy without decompensation is associated with an increase in sensitivity to digitalis. The tests were carried out on cats in which the left ventricle was markedly hypertrophied as a result of artificially produced aortic insufficiency. It was found that the sensitivity to digitoxin and strophanthin was definitely increased, whereas it was normal in hearts with recently produced aortic insufficiency without hypertrophy.

In a further study Dieckhoff [5] performed an interesting series of experiments on cats' hearts, using Starling's heart-lung preparation. When aortic insufficiency is produced by injuring a single cusp of a valve, the ability of the heart to do work is markedly reduced below normal, whereas if the valvular injury is of long standing (one hundred

4. Dieckhoff, J.: Digitoxin-Strophantin-Empfindlichkeit aortenklappeninsuffizienter Herzen mit und ohne Hypertrophie, Arch. f. exper. Path. u. Pharmakol. **182**:285, 1936.

5. Dieckhoff, J.: Leistungsfähigkeit aortenklappeninsuffizienter Herzen ohne und mit Hypertrophie im Herz-Lungen-Präparat (nebst Digitalisierungseffekten), Arch. f. exper. Path. u. Pharmakol. **182**:268, 1936.

to one hundred and fifty-four days) and accompanied with cardiac hypertrophy, the ability to do work approaches that of a normal heart. After injury to two aortic cusps the ability of the heart to do work is severely reduced, and this ability is not appreciably raised, even after passive hypertrophy. It was found that a heart with a fresh defect of the aortic valve which was made functionally complete by means of an ingenious artificial valve behaved similarly to a normal heart-lung preparation. If a heart that was hypertrophied as a result of long-standing valvular injury was made functionally complete by means of an artificial valve, it was capable of more work than a normal heart.

Other papers on physiology and experimental pathology [6] cannot be mentioned in detail, because of considerations of space.

ROENTGENOLOGY

The exhibition last year of excellent cineroentgenograms aroused great interest. Progress in cineroentgenography has been slow because of many serious difficulties.[7] The fundamental difficulty lies in the fact that x-rays will not refract in the manner of light rays, thereby making it impossible to focus them on a photographic film. Consequently it is necessary either to use a film of sufficient dimension to contain a natural-sized image of the object to be pictured or to photograph the image produced on a fluorescent screen. The former, so-called direct, method is being utilized by van de Maele and by others, while the latter, or indirect, method is being used by Djian,[8] by Reynolds and by Janker. Reynolds [7] has described his experiments and the many improvements in apparatus and technic made from time to time which have at last made indirect cineroentgenography a really practical achievement. At present it is impossible correctly to evaluate the many and far-reaching potentialities of this procedure. It should prove of immense value in the functional study of a moving, irregular, three-dimensional organ, such as the heart.

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6. Green, H. D.: The Coronary Blood Flow in Aortic Stenosis, in Aortic Insufficiency and in Arterio-Venous Fistula, Am. J. Physiol. **115**:94, 1936. Gauer, O.: Ueber Pulswellengeschwindigkeit in Aorta und Beinarterien des Menschen, Ztschr. f. Kreislaufforsch. **28**:7, 1936. Haynes, F. W.; Ellis, L. B., and Weiss, S.: Pulse Wave Velocity and Arterial Elasticity in Arterial Hypertension, Arteriosclerosis, and Related Conditions, Am. Heart J. **11**:385, 1936. Rothberger, C. J., and Zwillinger, L.: Ueber die Wirkung von Magnesium auf die Strophanthin- und die Barium-Tachykardie, Arch. f. exper. Path. u. Pharmakol. **181**:301, 1936. Bay, E. B.: The Work of the Left Ventricle in Aortic Insufficiency, J. Clin. Investigation **15**:643, 1936.

7. Reynolds, R. J.: Cineradiography, Fortschr. a. d. Geb. d. Röntgenstrahlen **53**:602, 1936.

8. A copy of Djian's cineroentgenogram of the heart was demonstrated by H. B. Sprague before a small group of physicians in Boston.

Four years of study and experimentation with roentgenkymography [9] have confirmed some of the early enthusiasm regarding its use in cardiovascular disorders. It is an objective and accurate method for graphically recording the physiologic and pathologic movements of the heart and great vessels, and its usefulness includes accurate topographic identification of the cardiac chambers; additional aid in the diagnosis of certain diseases of the heart, pericardium and great vessels, and better evaluation of the tonicity and force of contraction of the left ventricle.

Faber and Kjaergaard,[9f] in an excellent article, have pointed out that there have long been published several experimental roentgenologic works on the function of the heart which seem to unsettle somehow the conceptions adopted by the physiologists. According to Starling, the increased influx of venous blood during diastole produces temporarily a dilatation of the ventricles of the heart, so that the muscle fibers are lengthened prior to systolic contraction. This has been termed the physiologic dilatation of the heart, and many physiologists subscribe to this theory. During the past thirty-four years the results of numerous roentgenographic studies of the working heart have been incompatible with this theory. These studies have shown that in healthy persons there is usually a reduction in the size of the heart immediately after exercise. Occasionally there were found to be slight increases in size, but any considerable dilatation of the heart after maximal exertion occurs only when the myocardium is seriously affected.

The authors just mentioned made kymographic examinations of the hearts of 50 healthy young subjects during brief severe work. It was found that brief work produces changes in the heart similar to those that are demonstrable after more protracted work. These are increase of the rate of the beat and increase in the power of the individual contractions, associated with a rise of the blood pressure and a diminution in size of the heart both in systole and in diastole. The amplitude of excursion of the left ventricle increases significantly, and the same is true in a lesser degree for the right ventricle, which presumably accounts for the increased beat volume.

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9. (*a*) Heier, H.: Herzwandveränderungen im Flächenkymogramm, Fortschr. a. d. Geb. d. Röntgenstrahlen **53**:895, 1936. (*b*) Delherm, L., and Fischgold, H.: Quatre années de radiokymographie cardiovasculaire, ibid. **53**:223, 1936. (*c*) Scott, W. G., and Moore, S.: The Construction of Roentgenkymographs and Kymoscopes, Radiology **26**:622, 1936. (*d*) Roentgenkymography in Diseases of the Heart: A Relatively New and Efficient Aid in Diagnosis, J. A. M. A. **107**: 1951 (Dec. 12). (*e*) Hirsch, I. S., and Gubner, R.: Application of Roentgenkymography to the Study of Normal and Abnormal Cardiac Physiology, Am. Heart J. **12**:413, 1936. (*f*) Faber, B., and Kjaergaard, H.: Kymographic Studies on the Influence of Brief Muscular Work upon the Heart Function, Acta med. Scandinav. **89**:537, 1936.

It is evident from this and other studies that the increase of the beat volume in the working heart cannot be due to the increased diastolic dilatation but that it is due to an increased emptying power and a decrease in the volume of the heart during rest. The idea of passive dilatation of the heart as a cause of the increased minute volume is therefore, in the authors' opinion, to be replaced by a more active conception of the compensatory power of the heart and the increased beat volume.

Evans [10] has written the best account in the English language of the course of the esophagus in health and in disease of the heart and great vessels. The natural pliancy and intimate relationship of the esophagus to the heart and great vessels explains how readily its course may be altered by disease in these structures. These alterations together with the roentgenographic anatomy of the normal esophagus have been well described. It is our object to present this work in sufficient detail to be of practical value; unfortunately, it is not feasible to reproduce the illustrations.

A marmalade-flavored suspension of barium sulfate and another palatable preparation of barium sulfate were found especially suitable opaque meal substances. The position of choice for roentgenoscopy, with due regard to practicability, was found to be with the patient's arm raised and the hand placed on the head. Examination was always carried out in the three conventional positions—anterior, right oblique and left oblique.

Four esophageal curves or impressions can be seen in the healthy subject, and according to the viscus producing them, they have been designated as the impressions of the aortic arch, the left bronchus, the left auricle and the descending aorta. An impression caused by the left ventricle can sometimes be seen in the left oblique position. The contour of each curve alters when the patient is rotated to the right or to the left, and there is an optimal point at which each curve can be portrayed.

The impression of the aortic arch is produced by that portion of the arch which has commenced to descend. The concavity of the curve is directed to the left, is about 3 cm. long and, although seen in all three positions, is best seen in the anterior and in the right oblique position. Evans constructively criticizes Kreuzfuchs' method of determining the diameter of the aortic arch (distance from the aortic impression to the opposite border of the aortic shadow) by discussing variables which sometimes invalidate it.

10. Evans, W.: The Course of the Oesophagus in Health, and in Disease of the Heart and Great Vessels, Medical Research Council, Special Report Series, no. 208, London, His Majesty's Stationery Office, 1936.

In congenital dextrocardia the concavity of the impression of the aortic arch is directed toward the right and the other esophageal impressions also are reversed. In dextroposition of the aorta in the absence of dextrocardia, the impression of the aortic arch is directed toward the right, but the remaining esophageal impressions are unaltered.

In syphilitic aortitis the impression of the aortic arch may be displaced and elongated, and the diameter of the aorta may be increased. Changes limited to the ascending aorta or to the first portion of the aortic arch seldom disturb the impression. If the displacement is well marked and to the right in the anterior position, the aortic dilatation has occurred in the descending portion of the arch and chiefly to the right. If the impression is elongated without displacement and the aortic prominence is mostly to the left, the aortitis is situated in the descending portion of the arch and the upper part of the descending aorta. The effects of atheroma and hypertension on the impression of the aortic arch must be excluded before the changes are attributed to aortitis.

The impression of the aortic arch is clearly seen in all three positions and often is elongated in the anterior position if atheroma of the aorta is present. The dense aortic shadow in relation to the curve of the barium appears like a ball in a socket.

Deformity of the impression of the aortic arch may be produced by carcinomatous bronchial glands, goiter, aneurysm of the innominate artery and other conditions.

The impression of the left bronchus on the esophagus commences immediately below the impression of the aortic arch and is from 2 to 3 cm. long. It is poorly seen in the anterior position and best seen in the right oblique position, where the concavity of the curve is in the same direction as the impression of the aortic arch; in the left oblique position the concavity of the curve is oppositely directed to the impression of the aortic arch. Alteration of the curve of the left bronchus is not a frequent finding in cardiovascular disease, because of the rigidity of the bronchus which produces the impression. Accentuation of the curve may result from mitral stenosis but not from enlargement of the pulmonary artery. The impression of the left bronchus is the curve of least clinical importance.

In normal persons the impression of the left auricle is usually visible in the anterior position as a slight and gradual curve, with its concavity directed to the left. This impression is seldom seen in the left oblique position but is well seen in the right oblique position, as a gentle curve, 5 or 6 cm. long, with the concavity directed anteriorly. In an adult with a long and narrow thorax this curve may disappear during deep inspiration, but in a child it assumes such prominence that this finding should be judged with caution.

In mitral stenosis with slight enlargement of the left auricle a study of the impression of the left auricle in the anterior position is seldom decisive, because the chief esophageal displacement is backward; even in the right oblique position it is often difficult to say whether the curve is normal or abnormal. Some help is derived from a study of the upper segment of the curve, because abruptness of this portion is caused by the atrial prominence of the left auricle. With moderate or marked distention of the left auricle, the esophagus is seen in the anterior position to be displaced to the right and in the right oblique position to be displaced backward.

With enlargement of the left ventricle, the impression of the left auricle may be altered in a similar manner to that seen in enlargement of the left auricle. With enlargement of the left ventricle, however, the impression is seen in both oblique views, and the alteration is in the lower portion of the curve.

In aneurysm of the descending aorta the curve of the deformed left auricle is best seen in the left oblique position.

The impression of the descending aorta in the healthy subject is a gentle curve situated just above the diaphragm, with its concavity to the left in the anterior and in the left oblique position and a little to the right in the right oblique position. Its chief significance lies in the demonstration of changes in this portion of the aorta caused by syphilis and atheroma. Aneursym displaces the esophagus forward and to the left. Atheroma, with resulting elongation of the descending aorta, may be declared by elongation, by increased depth of the impression and, of course, by increased density of the aorta.

Parkinson and Bedford [11] have described a translucent triangle surmounting the aortic arch, which may be seen in the roentgenogram of the chest in the left oblique position. It is proposed as a landmark, additional to the aortic window, to simplify roentgenographic measurement of the aorta and identification of certain other structures in the thorax. The right border of the aortic triangle is formed by the left subclavian artery, the left border by the spine and the base by the arch of the aorta.

This triangle is diminished by elevation, elongation or dilatation of the aortic arch; it is enlarged by conditions which lower the aortic summit and by emphysema. It is often possible to determine the diameter of the aorta by measuring the distance between the base of the aortic triangle and the upper limit of the aortic window.

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11. Parkinson, J., and Bedford, D. E.: The Aortic Triangle: A Radiological Landmark in the Left (or II) Oblique Position, Lancet **2**:909, 1936.

McGinn and White [12] and Kautz and Pinner [13] have emphasized the importance of epicardial fat in roentgen studies of the heart. The chief importance lies in nonrecognition, which may lead to a considerable error in the roentgenographic measurement of the size of the heart.

ELECTROCARDIOGRAPHY

Recent interest in electrocardiography has centered around the study of chest leads. That they are valuable may be taken as an established fact, and their routine use should be encouraged.

There is still some difference of opinion regarding the optimal placing of the electrodes. Undoubtedly, more work is necessary before this question can be settled to the satisfaction of all. We see no sufficient reason yet to alter our earlier statement that for routine examination it seems wise to use a single chest lead (lead IV) with electrodes applied to the area over the cardiac apex and to the left leg. Rarely it may be necessary to apply the chest electrode in other positions over the thorax. It has been shown and reemphasized recently [14] that when the chest electrode is applied just to the right of the sternum at the level of the third rib, the resulting curves are especially suitable for the interpretation of auricular components, and when the electrode is applied over the apical area of the heart, the resulting curves are especially suitable for the interpretation of ventricular components of the electrocardiogram. The so-called indifferent electrode is usually placed on the left leg when the chest lead is taken, although Wolferth and Wood have said that they feel that something may be lost unless this electrode is placed on the back.

Because the "precordial" electrocardiogram is determined largely by the variations in potential from the chest electrode, any considerable shift in location of this electrode or in the position of the heart will affect to an important degree the resulting curves. Hence criteria for the normal deflections in lead IV are defined with difficulty. The initial ventricular deflection usually consists of a sharp downward deflection (Q), 1.5 mm. or more in amplitude, followed by a sharp upward deflection (R), 1.5 mm. or more in amplitude. The ST segment is usually very short, beginning at or slightly below the iso-electric

12. McGinn, S., and White, P. D.: Epipericardial Fat: Its Nonrecognition a Common Cause of Error in X-Ray Measurement of Heart Size, J. A. M. A. **107**:200 (July 18) 1936.

13. Kautz, F. G., and Pinner, M.: Extrapericardial Fat Bodies, Am. J. Roentgenol. **35**:40, 1936.

14. Lian, C., and Golblin, V.: Intéret nosographique et pratique de la dénervation précordiale auriculaire, Ann. de méd. **29**:721, 1936. Hecht, H.: Brustwandableitungen in der klinischen Elektrokardiographie, Deutsches Arch. f. klin. Med. **179**:1, 1936.

level and quickly merging with T, which in adults is inverted and from 2 to 10 mm. in amplitude. Absence of the Q wave or displacement of the ST segment is the most significant abnormality which may occur; alterations in the T wave are more commonly seen but are of lesser significance. It has been known for some time and reemphasized lately [15] that in children the T wave is usually upright or diphasic but may be inverted as it is in normal adults.

Lead IV has shown its greatest usefulness in the diagnosis and prognosis of coronary heart disease, especially coronary occlusion.

After infarction of the anterior wall of the heart the first electrocardiographic change is usually a lowering of the ST segment in lead IV. This is followed by a marked decrease in amplitude or abolition of Q and by an upward deflection of T in the same lead. During recovery the ST segment usually reverts to the normal position; the T wave may or may not become inverted again, but the Q wave rarely reappears. Not only may the electrocardiographic alterations in lead IV be the first to declare the presence of acute infarction of the anterior wall, but they may persist, even though all other electrocardiographic evidence of infarction has disappeared. For patients with angina pectoris in whom there is no clinical evidence of previous coronary thrombosis, lead IV may give the only electrocardiographic evidence that myocardial infarction has taken place.[16]

After infarction of the posterior basal portion of the heart there is usually no significant alteration in lead IV. Sometimes, however, the first sign of infarction is seen in an upward displacement of the ST segment in this lead. Occasionally there are changes in the T wave; T may become deeper than normal or upright.

There is some current interest, with little publication as yet, in myocardial infarction which produces inversion of T in lead I or leads I and II, an upright T wave in lead IV and persistence of Q in lead IV. For patients showing these electrocardiographic abnormalities there is apparently a good prognosis, and as yet there is little or no information obtained at autopsy. It is probable than the infarct causing such changes is small and located laterally or marginally.

In rheumatic heart disease the T wave in lead IV may become upright. Because an upright, diphasic or polyphasic T wave in this

15. (*a*) Rosenblum, H., and Sampson, J. J.: A Study of Lead IV of the Electrocardiogram in Children with Especial Reference to the Direction of Excursion of the T-Wave, Am. Heart J. **11**:49, 1936. (*b*) Rabinow, M.; Katz, L. N., and Bohning, A.: The Appearance of the T-Wave in Lead IV in Normal Children and in Children with Rheumatic Heart Disease, ibid. **11**:88, 1936.

16. Levine, S. A., and Levine, H. D.: An Electrocardiographic Study of Lead IV, with Special Reference to the Findings in Angina Pectoris, Tr. A. Am. Physicians **1**:303, 1935.

lead is common for normal children, single tracings in individual cases add no valuable information.[16b] Serial electrocardiograms may supply suggestive data, but it cannot be emphasized too strongly that it is difficult to take serial records which are strictly comparable, for the reasons just given.

Lead IV of the electrocardiogram may be abnormal in cases of pericarditis, but only rarely should these abnormalities be confused with those seen in coronary heart disease. In fact, lead IV frequently may be helpful in the differential diagnosis.

The electrocardiogram in acute cor pulmonale (and perhaps other instances of enlargement of the right ventricle) apparently resembles the electrocardiogram in infarction of the posterior wall of the heart, except that the T wave in lead IV is upright.

Digitalis in large doses may affect lead IV; this is seen in the elevation of the ST segment and even elevation of the T wave itself.

In the various other types of cardiac disease lead IV apparently is not of great value. Further study, however, may require alteration of this point of view.

In the understanding of the arrhythmias lead IV is not necessary. The only exception to this is in regard to the chest lead which yields curves illustrating particularly auricular activity. It should be emphasized that when defects in intraventricular conduction are present, lead IV is usually bizarre and cannot be interpreted in the usual manner.

Two of the numerous other electrocardiographic studies[17] will be reviewed.

Heard, Burkley and Schaefer[17a] obtained electrocardiograms from 11 human fetuses, using direct leads. The fetuses were from 9½ to 25 weeks old. The electrocardiographic deflections in both the limb and the chest lead resembled those of adults. Normal sinus rhythm was present in all, although it was interrupted in some cases by various

17. (*a*) Heard, J. D.; Burkley, G. G., and Schaefer, C. R.: Electrocardiograms Derived from Eleven Fetuses Through the Medium of Direct Leads, Am. Heart J. **11**:41, 1936. (*b*) Hamburger, W. W.; Katz, L. N., and Saphir, O.: Electrical Alternans: A Clinical Study with a Report of Two Necropsies, J. A. M. A. **106**:902 (March 14) 1936. (*c*) Katz, L. N., and Robinow, M.: The Appearance of the Electrocardiogram in Relation to the Position of the Heart Within the Chest, Am. J. M. Sc. **192**:556, 1936. (*d*) Tigges, F.: Das Elektrokardiogramm bei Hypoxämie, Ztschr. f. Kreislaufforsch. **28**:225, 1936. (*e*) Berliner, K.: The Effect of Calcium Injection on the Human Heart, Am. J. M. Sc. **191**:117, 1936. (*f*) Schwartz, S. P.: Studies on Transient Ventricular Fibrillation: IV. Observations on the Clinical and Graphic Manifestations Following the Revival of the Heart from Transient Ventricular Fibrillation, ibid. **192**:808, 1936. (*g*) Graybiel, A., and White, P. D.: Complete Auriculo-Ventricular Dissociation: A Clinical Study of Seventy-Two Cases with a Note on a Curious Form of Auricular Arrhythmia Frequently Observed, ibid. **192**:334, 1936. (*h*) Delius, L., and Opitz, E.: Ueber Veränderungen des Elektrokardiogramms bei Morbus Addison, Deutsches Arch. f. klin. Med. **178**:1, 1936.

arrhythmias. Slight sinus arrhythmia was present in 4 cases. Comparison of the conduction time in the human adult with that in the fetus shows that in the latter to be only slightly shorter. The several waves are described in detail.

Hamburger, Katz and Saphir [17b] have described 2 cases of so-called electrical alternans. This disorder is extremely rare; and while it may appear in several forms, the underlying mechanism is probably identical in all instances. Electrical alternation is a sign of grave prognostic significance.

CONGENITAL HEART DISEASE

Arkin [18] has presented 6 cases of a congenital aortic anomaly, with postmortem observations in 2 cases, consisting of total persistence of the right aortic arch, combined with persistence of the left aortic arch in the form of the left subclavian artery, an isthmus stenosis and a diverticulum of the aortic arch (left descending dorsal aortic root). The right arch was situated behind the esophagus and the left arch in front of the trachea.

According to Arkin:

> The cases all present characteristic x-ray findings which are: (1) a shadow to the right of the sternum, running upward to the head of the right clavicle, with a distinct systolic pulsation; (2) slight displacement of the trachea, and definite displacement of the esophagus to the left; (3) absence of the normal aortic knob on the left side, or only a small shadow of the descending arch on the left side; in some cases two aortic knobs, one on each side; (4) in the right oblique position the aortic knob lies behind the trachea and esophagus, both of which are displaced forward and to the left (most characteristic of all is the circular forward displacement of the esophagus by the arch of the aorta); (5) shadow of the diverticulum either in the retroesophageal knob or in the descending arch on the left side; (6) in the left oblique position a wide shadow of the ascending aorta to the right of the trachea and evidence that the aortic arch runs behind the esophagus to reach the left side. . . .
>
> The following clinical signs were found in the six cases: (1) dullness to the right of the sternum, (2) visible systolic pulsation in the second and third right intercostal spaces, (3) palpable, strong pulsation in the right supraclavicular fossa, (4) maximum intensity of the aortic sounds in the region of the head of the right clavicle, (5) slight displacement of the trachea to the left, (6) tracheal tug, (7) delay in passage of the stomach tube at the level of the third dorsal vertebra, with transmitted pulsation from the arch of the aorta.

Taussig [19] has presented in detail reports of 2 cases of congenital malformation of the heart due to defective development of the right

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18. Arkin, A.: Double Aortic Arch with Total Persistence of the Right and Isthmus Stenosis of the Left Arch: A New Clinical and X-Ray Picture, Am. Heart J. **11**:444, 1936.

19. Taussig, H. B.: The Clinical and Pathological Findings in Congenital Malformations of the Heart Due to Defective Development of the Right Ventricle Associated with Tricuspid Atresia or Hypoplasia, Bull. Johns Hopkins Hosp. **59**: 435, 1936.

ventricle associated with atresia or hypoplasia of the tricuspid valve. For the first time this congenital abnormality has been correctly diagnosed ante mortem, and the clinical findings described are sufficiently characteristic to determine a new clinical syndrome.

A description of this abnormality follows:

The central feature in this congenital malformation is the diminutive size of the right ventricle. The associated malformations can be postulated from the fact that the right ventricle does not function. The failure of the ventricle to function means that neither the tricuspid valve nor the pulmonary valve can function, and hence they are either atresic or markedly hypoplastic. Furthermore, it means that the only way for the blood to escape from the right auricle is through some defect in the interauricular septum. The extent of this defect determines whether the heart functions as a biloculate or triloculate heart.

Clinically, the malformation is associated with persistent cyanosis and no murmurs. The diagnosis is established through the recognition of the diminutive size of the right ventricle. This condition can be recognized in the roentgenogram by the peculiar outline of the cardiac shadow. In the A-P view, because of the absence of the pulmonary conus, the upper contour of the cardiac shadow immediately to the left of the sternum has a concave instead of a convex outline. In the left anterior oblique position the small size of the right ventricle is indicated by the absence of cardiac shadow anterior to that of the aorta. These observations are substantiated by the electrocardiagam which shows a left axis deviation.

The differentiation between a functionally biloculate and a triloculate heart depends upon the size of the interauricular septal defect. If there is free communication between the two auricles, i. e., functionally a biloculate heart, physical examination yields no additional positive findings. In contrast, when the interauricular septum is well formed, it causes obstruction to the outflow of blood from the right auricle. Under these circumstances, the auricular pulsation is transmitted to the liver and is readily palpable at its margin. It is this pulsation at the edge of the liver occurring in conjunction with a diminutive right ventricle which distinguishes a functionally triloculate from a functionally biloculate heart.

Abbott [20] has published an excellent monograph on congenital cardiac disorders.

RHEUMATIC HEART DISEASE

The possible relationship between the hemolytic streptococcus and rheumatic fever is still much under discussion.[21] Undoubtedly an attack of acute rheumatism is often preceded by infection of the upper respiratory tract with the hemolytic streptococcus. After the infection of the respiratory tract there may be a symptom-free period of a few days or weeks before the rheumatic symptoms are apparent. Many

20. Abbott, M. E.: Atlas of Congenital Cardiac Disease, New York, American Heart Association, 1936.

21. Coburn, A. F.: Observations on the Mechanism of Rheumatic Fever, Lancet **2**:1025, 1936.

investigators have said that they believe this sequence is the rule and consider it as partial proof of the intimate if not etiologic rôle of the hemolytic streptococcus. This is supported by a large body of immunologic evidence, which shows there is often a relationship between development and intensity of the immune response to hemolytic streptococci and the rheumatic process.

On the other hand, rheumatic fever develops in many patients who have no history of previous infection of any kind and whose serum shows no abnormal concentration of streptococcic immune bodies. Furthermore, it has been observed clinically and shown experimentally that rheumatic fever may be reactivated by events other than streptococcic infection. Without reviewing this subject further, it may be stated categorically that the evidence is insufficient to establish a causal connection between streptococcic infection and rheumatic fever.

The concept that rheumatic fever may be due to the combined influence of vitamin C deficiency and infection is finding little support either clinically or experimentally. It has, however, stimulated interest in the study of vitamin C metabolism in this disease.[22] Criteria for a diagnosis of latent scurvy are being worked out, and the relation of infection and fatigue to storage and excretion of vitamin C is being investigated.

The recent investigations suggesting that a filtrable virus may play an etiologic rôle in rheumatic fever were reviewed last year in some detail. Swift [23] has pointed out that if a virus were etiologically significant in rheumatic fever but required some synergic influence for its activation, this would explain a number of features of the disease. Here again the whole truth is unknown and must await further study.

The relationship between rheumatic fever and rheumatoid arthritis has been ably discussed by Dawson and Tyson.[24] This problem is discussed on the basis of (1) familial relationship, (2) geographic distribution, (3) initiating factors, (4) seasonal incidence, (5) age incidence and clinical manifestations in different age periods and (6) pathologic similarities and immunologic findings. The strongest evidence that the two diseases are intimately related and possibly different manifestations of the same fundamental pathologic process is found in those numerous cases of a transitional nature in which it is impossible to decide which disease is present. Naturally, a final understanding cannot be reached until the etiology of both diseases is established.

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22. Rinehart, J. F.: An Outline of Studies Relating to Vitamin C Deficiency in Rheumatic Fever, J. Lab. & Clin. Med. **21**:597, 1936.

23. Swift, H. F.: The Nature of Rheumatic Fever, J. Lab. & Clin. Med. **21**:551, 1936.

24. Dawson, M. H., and Tyson, T. L.: The Relationship Between Rheumatic Fever and Rheumatoid Arthritis, J. Lab. & Clin. Med. **21**:575, 1936.

Gross and his co-workers [25] have continued their important studies on certain clinicopathologic aspects of rheumatic heart disease. New macroscopic and microscopic data on the development of the rheumatic lesions in the valves and in their rings, together with a discussion of the factors which determine the spread of infection and the localization of lesions, have been presented. In approximately 66 per cent of 60 cases of active rheumatic fever there were lesions in the bundle of His. The nature of these lesions was discussed. The gross and microscopic pericardial lesions in 87 cases of active and inactive rheumatic fever were discussed. It was possible to divide the cases into five clinical groups, and the pathologic lesions as a whole fell into three more or less characteristic histologic patterns.

Recent information regarding the evaluation of rheumatic fever has changed to an important degree the clinical conception of this illness. It is now recognized that in the acute or subacute stages many structures, in addition to the heart and joints, may show manifestations of disease.[26] Furthermore, it has been shown that in the early decades of life a significant degree of rheumatic heart failure is, with few exceptions, due to active disease. Consequently, signs of mild infection have been carefully sought for and studied. Most of the clinical signs have long been known but have not received the general acceptance or the proper emphasis they deserve. The practical value of certain laboratory tests, especially sedimentation tests of the blood and electrocardiography, are well established.

A symptom sometimes difficult to evaluate in children is pain in the legs. Shapiro [27] has attempted to differentiate between rheumatic and nonrheumatic pain on the basis of clinical observation. It was found that rheumatic children with pain in the legs usually point to the joints as the location of the maximum pain; at one time or another all the extremities are involved; the patients complain mostly during the day, especially on first arising; the pain is intensified on motion; there is difficulty in walking, and a limp is frequently noted. On the other

25. Gross, L., and Friedberg, C. K.: Lesions of the Cardiac Valves in Rheumatic Fever, Am. J. Path. **12**:855, 1936; Lesions of the Cardiac Valve Rings in Rheumatic Fever, ibid. **12**:469, 1936. Gross, L., and Fried, B. M.: Lesions in the Auriculoventricular Conduction System Occurring in Rheumatic Fever, ibid. **12**: 31, 1936. Friedberg, C. K., and Gross, L.: Pericardial Lesions in Rheumatic Fever, ibid. **12**:183, 1936.

26. Bourne, G.: Acute Rheumatic Meningitis, Brit. M. J. **2**:1017, 1936. Wolffe, J. B., and Brim, C. J.: The Abdominal Syndrome of Rheumatic Disease in Childhood, Am. J. Dis. Child. **52**:296 (Aug.) 1936. Coburn, A. F., and Kapp, E. M.: Observations on the Development of the High Blood Sedimentation Rate in Rheumatic Carditis, J. Clin. Investigation **15**:715, 1936.

27. Shapiro, M. J.: The Natural History of Childhood Rheumatism in Minnesota, J. Clin. & Lab. Med. **21**:564, 1936.

hand, nonrheumatic children with pains in the legs locate the pain in the muscles of the leg and are unable to define any point of maximal discomfort; the upper extremities are rarely involved; the children complain chiefly after going to bed and sometimes awake crying two or three hours after going to sleep, and motion, massage and heat cause the pain to disappear.

Bland, Jones and White [28] have studied 1,000 young patients with the physical signs of rheumatic valvular heart disease during the first ten years after the onset of rheumatic infection and have observed a regression of these signs in a considerable number and a total disappearance of all clinical evidence of cardiac disease in 83. In a few instances cardiac dilatation during the stage of acute rheumatism may have been responsible for the murmurs heard, and the decrease in the size of the heart during recovery may have been responsible for their disappearance. These authors never observed the disappearance of either a very loud diastolic murmur ending in a loud crescendic presystolic roll or a loud aortic diastolic murmur when the peripheral circulatory signs of free aortic regurgitation were present.

Regarding the treatment of active rheumatism and its manifestations, the chief interest at present is in fever therapy.[29] This interest began a few years ago by a chance observation. A child suffering from chorea was given phenylethylhydantoin for sedation. A typical reaction developed, with a rash and fever. Surprisingly, the choreiform movements disappeared in a short time. It was soon discovered that the essential factor was the rise in temperature. Many hundreds of patients with chorea have now been treated with some form of fever therapy. According to the published results, the course of the chorea can be greatly shortened. Apparently only rarely does a patient fail to respond to this treatment, and unfavorable effects have been negligible.

Now chorea is a symptom and is associated with other symptoms of active rheumatic infection in all save a small percentage of cases. Consequently the effect of fever therapy on rheumatic carditis also was necessarily observed. Reports indicate that the presence of sub-

28. Bland, E. F.; Jones, T. D., and White, P. D.: Disappearance of the Physical Signs of Rheumatic Heart Disease, J. A. M. A. **107**:569 (Aug. 22) 1936.

29. Sutton, L. P., and Dodge, K. G.: Fever Therapy in Chorea and in Rheumatic Carditis With and Without Chorea, J. Lab. & Clin. Med. **21**:619, 1936. Neymann, C. A.; Blatt, M. L., and Osborne, S. L.: The Treatment of Chorea Minor by Means of Electropyrexia, J. A. M. A. **107**:938 (Sept. 19) 1936. Barnacle, C. H.; Ewalt, J. R., and Ebaugh, F. G.: Artificial Fever Treatment of Chorea: Preliminary Report, ibid. **106**:2046 (June 13) 1936. Weisman, D., and Leslie, C.: Treatment of Sydenham's Chorea with Typhoid Paratyphoid Vaccine, New York State J. Med. **36**:1587, 1936.

acute rheumatism is not a contraindication to this treatment. In fact, there is suggestive evidence that the fever has a beneficial effect not only on the chorea but on the rheumatic carditis itself. Undoubtedly there will be much further investigation along this line. At present the experience with fever therapy in active rheumatism, apart from chorea, has been too limited to allow any conclusion to be drawn.

Marinesco and his co-workers [30] have made a careful clinical and anatomic study of a patient with chorée molle, or "limp chorea." An abstract of the case report follows:

A girl aged 15 years began to complain of involuntary movements of the hands eleven months after an attack of acute polyarticular rheumatism. Her illness was rapidly aggravated, and within a month she could neither walk nor talk, because of involuntary movements, which involved most of the skeletal muscles. This was soon followed by a paralytic state ("limp chorea") which was associated with severe toxic infection and acute endocarditis. The reflexes, which had been normal, disappeared, and the patient gradually went into coma and died. Necropsy revealed mitral endocarditis, various lesions in the central nervous system and marked degenerative changes in the muscles. It was thought that the hypotonia or paralysis was not due to lesions in the nervous system but probably to lesions in the muscles themselves.

BACTERIAL ENDOCARDITIS

Welch, Murdock and Ferguson [31] used various methods to produce valvular lesions in rabbits with streptococci of the alpha or beta types which have the ability to show a diphtheroid-like phase on suitable mediums. Of the 35 rabbits tested, 7 showed lesions on the cardiac valves which resembled, grossly and microscopically, the vegetations seen in subacute bacterial endocarditis in human beings. These lesions were all on the left side of the heart, and all revealed short chains of streptococci and diphtheroid-like forms. Twelve of the 35 animals showed neither gross nor microscopic lesions on the cardiac valves; the remaining 16 showed lesions on the mitral or aortic valves that did not resemble the typical lesions of subacute bacterial endocarditis. These lesions were about 1 mm. in diameter and reddish and occurred along the line of closure or nearer the bases of the valves. Microscopic study revealed a few red blood cells and a few strands of fibrin adherent to the endothelium, which was swollen and in some instances broken. There was a mild cellular reaction, but suitably stained sections did not show bacteria. These nonbacterial lesions were thought to be caused by the streptococci which were injected into the rabbits and to represent the initial stage in the development of subacute bacterial endocarditis.

30. Marinesco, G.; Draganesco, S.; Axente, S., and Bruckner, I.: Etude anatomo-clinique d'un cas de chorée molle, Ann. de méd. **40**:397, 1936.

31. Welch, H.; Murdock, T. P., and Ferguson, J. A.: Subacute Bacterial Endocarditis Produced in Rabbits with Streptococci That Resemble Diphtheroids, J. Lab. & Clin. Med. **21**:1264, 1936.

Cornil, Mosinger and Jouve [32] made a careful histologic study of an Osler node removed twenty-four hours after its appearance in a case of typical subacute bacterial endocarditis. They confirmed the view that these nodules are not embolic phenomena but the fusion of a series of small inflammatory lesions involving the minute vessels and the surrounding tissues.

Riesman, Kolmer and Polowe [33] reported 4 cases of subacuate bacterial endocarditis in which splenectomy was performed. In each instance the operation was well borne, and the authors said they felt sure that life was prolonged and made more comfortable. It is suggested that this procedure be given consideration in the symptomatic treatment of this disease. In the discussion of this paper at the meeting of the Association of American Physicians, Lord Horder said he felt that there was no justification for such treatment.

ARTERIAL HYPERTENSION

The question of hyperepinephrinemia and hypertension has received renewed consideration. Kuré and his co-workers [34] found that stimulation of the splanchnic nerves in dogs always causes an increase in blood pressure and hyperepinephrinemia. These two effects usually run parallel but occasionally they are separated; that is, the rise in blood pressure may be considerable yet the hyperepinephrinemia may be slight, or vice versa. They argued that in their experiments the increase in blood pressure even with slight hyperepinephrinemia must have been related to the adrenal glands, because all other structures which might have released a pressor substance were cut out of the circulation. They attempted to explain this phenomenon on the basis of experiments by Rusznyák and Szent-Györgyi, who have shown that the pressor substance elaborated by the adrenal glands is not epinephrine itself but its precursor novo-epinephrine. This epinephrine ester has a far stronger pressor action than epinephrine. Thus, if it remains unsplit for some time, such a circumstance could explain the rise in blood pressure, with only slight hyperepinephrinemia, because epinephrine combined with lipoids probably is not detectable as epinephrine. Kuré and his associates said they believe that hyperfunction of the adrenal glands cannot be ruled out as the cause of hypertension simply because hyperepinephrinemia is not found.

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32. Cornil, L.; Mosinger, M., and Jouve, A. X.: Contribution à l'étude histologique du nodule d'Osler, Ann. d'anat. Path. **13**:675, 1936.

33. Riesman, D.; Kolmer, J. A., and Polowe, D.: Splenectomy in Treatment of Subacute Bacterial Endocarditis, Am. J. M. Sc. **192**:475, 1936.

34. Kuré, K.; Okinaka, S.; Ohshima, K.; Shimamoto, T., and Okamura, D.: Blutdrucksteigerung bei Nebennierenreizung und Hyperadrenalinämie, Klin. Wchnschr. **15**:477, 1936.

Pickering and Kissin [35] presented evidence against the view that essential hypertension and chronic nephritic hypertension are due to hyperepinephrinemia. They found the susceptibility of the minute facial vessels to epinephrine and their ordinarily dilated state in essential and their sometimes unconstricted state in nephritic hypertension facts which do not reconcile with the view that the raised blood pressure is due to hyperepinephrinemia. In regard to the claim that patients with chronic nephritic hypertension are abnormally sensitive to epinephrine, they found nothing in their tests to support this view.

Pickering [36] observed the changes in the arterial blood pressure produced in anemic subjects by transfusion of blood from patients with essential hypertension. These changes were found to be slight and no greater than those produced by transfusion of an equal value of normal blood. He said he feels that this result is opposed to the idea that the raised blood pressure in essential hypertension is due to excess of pressor or deficit of depressor substances in the circulating blood.

In considering the relationship between renal disorders and hypertension, it is of the greatest significance that permanent arterial hypertension may be produced experimentally in dogs by renal ischemia without material decrease in renal function. In experimental hypertension Wood and Cash [37] find that the rise in blood pressure is not proportionate to the degree of renal insufficiency and that marked hypertension does not necessarily accompany even severest insufficiency. Thus, while hypertension is in some way related to reduction or alteration of renal tissue, it is largely independent of renal function. Thus far there has been no explanation of the exact mechanism by which this hypertension results. It is probably of chemical origin, because it has been shown experimentally that the renal nerves play no part in its production. This view has received support from the clinical studies of Pickering.[38] He has shown that not only in chronic nephritis but in essential hypertension the factor causing vasoconstriction is non-nervous. On the other hand, the temporary hypertension associated with acute nephritis is probably of nervous origin in most cases.

The controversy still goes on regarding the rôle of the pituitary gland in arterial hypertension. Marañón and Domenech,[39] from data

35. Pickering, G. W., and Kissin, M.: The Effects of Adrenaline and of Cold on the Blood Pressure in Human Hypertension, Clin. Sc. **2**:201, 1936.

36. Pickering, G. W.: The Effect of Introducing Blood from Patients with Essential Hypertension into Other Human Subjects, Clin. Sc. **2**:185, 1936.

37. Wood, J. E., and Cash, J. R.: Experimental Hypertension—Observations on Sustained Elevation of Systolic and Diastolic Blood Pressure in Dogs, J. Clin. Investigation **15**:543, 1936.

38. Pickering, G. W.: The Peripheral Resistance in Persistent Arterial Hypertension, Clin. Sc. **2**:209, 1936.

39. Marañón, G., and Domenech, F.: Variations of Blood Pressure in Diseases of the Hypophysis, Brit. M. J. **2**:851, 1936.

they collected, made the categoric statement that the hypophysis has nothing to do with the regulation of blood pressure. However, they immediately went on to say that in Cushing's disease the high pressure may be explained by the concurrent hyperfunction of the adrenal glands. Jores [40] was equally emphatic in saying that overproduction of the adrenotropic hormone of the anterior lobe of the pituitary gland is the cause of the increased blood pressure in essential hypertension. This view is based on the discovery of a substance in the serum of hypertensive persons which calls forth alterations similar to those of the adrenotropic hormone of the hypophysis and which has similar chemical characteristics.

For some time the cold pressor test has been used for measuring the reactibility of the blood pressure. On the basis of this test Hines and Brown [41] have divided all subjects with normal blood pressure levels into two groups: (1) those with "normal" or minimal reactions and (2) those with "abnormal" or excessive reactions. They said they believe that essential hypertension affects only those in the second group, and the transition has been observed in 3 cases. It is pointed out, however, that essential hypertension may not affect all hyperreactors. Pickering and Kissin,[35] on the basis of a small series of observations, were unable to confirm the view that a relatively great rise of blood pressure in response to a cold stimulus is peculiar to potential or acquired essential hypertension.

In regard to the treatment of arterial hypertension, the chief interest still centers in the various operative procedures.[42] These procedures have as their basis either the reduction of the activity of the adrenal glands or the sympathetic denervation of a large vascular area or both. The evidence that the adrenal glands play a significant rôle in arterial hypertension is inconclusive except, of course, in the case of pleochromatic tumors of the glands; the evidence that abnormal nervous vasoconstriction is a factor in causing abnormally high blood pressure is likewise inconclusive, save in rare instances. In fact, the main body

40. Jores, A.: Die Bedeutung der Hypophyse für die Entstehung des Hochdruckes insbesondere der essentiellen Hypertonie, Klin. Wchnschr. **15**:841, 1936.

41. Hines, E. A., and Brown, G. E.: The Cold Pressor Test for Measuring the Reactibility of the Blood Pressure: Data Concerning Five Hundred and Seventy-One Normal and Hypertensive Subjects, Am. Heart J. **11**:1, 1936.

42. (*a*) Heuer, G. J.: The Surgical Treatment of Essential Hypertension, Ann. Surg. **104**:771, 1936. (*b*) Adson, A. W.; Craig, W. M., and Brown, G. E.: Surgery and Its Relation to Hypertension, Surg., Gynec. & Obst. **62**:314, 1936. (*c*) Smithwick, R. H.: The Value of Sympathectomy in the Treatment of Vascular Disease, New England J. Med. **216**:141, 1936. (*d*) Ritch, C. O.: Urologic Lesions Masked as Essential Hypertension, Illinois M. J. **70**:74, 1936. (*e*) Roch, M.; Martin, E., and Sciclounoff, F.: Les injections intraveineuses de solutions glucosées hypertoniques; leur action et leur emploi chez les brightiques hypertendus, Ann. de méd. **39**:286, 1936. (*f*) Palmer, R. S.: The Efficacy of Medical Treatment in Essential Hypertension, New England J. Med. **215**:569, 1936.

of evidence strongly suggests that in chronic nephritic and essential hypertension the high blood pressure is of nonnervous origin. As Pickering [38] has pointed out, although there is little doubt that vasoconstriction of nervous origin does constitute a considerable fraction of the peripheral resistance in permanent hypertension, just as it does in normal subjects, it probably does not constitute the abnormal factor responsible for the raised arterial pressure. If this is true, resection of the splanchnic nerves, for example, would lower the blood pressure simply by abolishing the normal nervous vasoconstrictor tone to a large vascular area. However, as Phemister has emphasized, the excision of normal structures, with abolition of normal physiologic processes, should not cure disease as does excision of pathologic structures. This is emphasized by the fact that the decrease in vascular tonus consequent to the destruction of sympathetic innervation is largely regained either by regeneration of the nerves or by the increased susceptibility of the denervated vessels to circulating hormones and possibly to other pressor bodies.

These considerations have been borne out fairly well in clinical practice. Heuer,[42a] in a carefully studied group of hypertensive patients, reported that section of the anterior roots cannot be expected to cause a permanent reduction of more than 25 per cent of the preexisting systolic and diastolic blood pressures. When the initial pressure is raised not far above normal, this operation may reduce it to within the normal range, but if the initial pressure is very high, a 25 per cent reduction is less significant. Symptomatic improvement, however, is usually marked. Heuer's results with section of the anterior roots are a little better than those of Adson,[42b] probably owing to better selection of patients, as the latter has pointed out.

Heuer's results with resection of the splanchnic nerves were disappointing, although Adson [42b] and Smithwick [42c] were encouraged with their results and said that it is the procedure of choice. Further observations will be necessary to evaluate the surgical treatment of permanent hypertension. In general, the results are disappointing. The fact that some patients benefit considerably indicates that a proper selection of patients might yield encouraging results.

CORONARY HEART DISEASE

Angina Pectoris.—Essex and his co-workers [43] have described an interesting series of observations on the flow in the coronary arteries in the the intact dog in response to a variety of stimuli, such as drugs, food and exercise. After a Rein thermostromuhr unit had been fixed around the circumflex artery, tests were made over periods as long as

43. Essex, H. E.; Herrick, J. F.; Baldes, E. J., and Mann, F. C.: Blood Flow in the Circumflex Branch of the Left Coronary Artery in the Intact Dog, Am. J. Physiol. **117**:271, 1936.

fourteen days. Every effort was made to determine the blood flow under as nearly normal conditions as could be devised. As a rule, the animal took food and water, ran about the laboratory and behaved in such a manner that a casual observer would not suspect the presence of the unit in the thorax.

Determinations of the blood flow were made on the quietly resting dog, and in a number of instances daily values were obtained that fell within the experimental error of the method (10 per cent). Epinephrine caused a transient augmentation in flow from two to four times the control values; the augmentation did not last longer than seven minutes in any of the tests, and, as a rule, the major effect terminated three minutes after the injection, thus paralleling the known effect of doses of epinephrine on the blood pressure of the dog.

Repeated observations indicated that glyceryl trinitrate in intravenous doses of 0.22 mg. resulted in a temporary increase in coronary blood flow, which at its maximum was about twice the control value. However, the increase was of short duration, since it usually was over four or five minutes after the injection. Within two minutes after the inhalation of amyl nitrite the coronary flow increased to about twice the control value. Although the animal continued to breathe the drug, the blood flow did not remain at twice the control level for more than two minutes, when it declined to a value from 20 to 30 per cent above the control. In one experiment a second ampule was administered six minutes after the effect of the first ampule had been dissipated. Only a slight elevation in coronary blood flow followed, which clearly indicated that the dog is refractory to a second dose given too soon after the first dose.

In response to appropriate doses of thyroxin, increases of coronary flow as great as 244 per cent above the control values were observed from forty-eight to ninety-six hours after the injection was given. An increase of coronary flow of as much as 84 per cent was observed during the digestion of food.

The effect of exercise on coronary blood flow was especially interesting. When the exercise was begun there was an immediate rise in coronary flow, which attained maximal values in about five minutes, after which it gradually subsided to a much lower level in the succeeding five minutes. The flow remained relatively steady at the lower level until the amount of exercise was increased, whereupon the flow again rapidly increased for about five minutes, after which it declined to a lower level, but remained above the second level reached during the previous increment in exercise. When exercise was stopped the flow rapidly fell to or below the values for controls.

The results of these studies are in general accord with those previously reported but have especial importance because of the less abnormal experimental conditions.

Mainzer and Josephthal [44] have undertaken a comprehensive consideration of the rules governing the localization and radiation of pain in angina pectoris. They began with some well known facts; they pointed out that anginal pain is characteristically located behind the sternum or in the precordial region, that the pain commonly radiates to the left and less commonly to the right, that the radiating pain may appear a little before the discomfort in the cardiac area, that in general the attacks are similar in a given person but dissimilar in various patients and that the radiation is frequently dependent on the strength of the attack, a weak attack causing slight substernal pain, a stronger attack causing substernal pain with radiation to the left arm and a still stronger attack causing substernal pain with radiation to both arms.

These remarkable characteristics of the radiation have been discussed by Daniélopolu. He showed, on embryologic grounds, that the left side of the heart is supplied chiefly by left-sided nerves and the right side of the heart by right-sided nerves. Hence, in ischemia of the left side of the heart any radiation of the pain should be to the left, and the greater frequency of left-sided radiation coincides with the greater incidence of left-sided coronary sclerosis. Daniélopolu said he considers that an anginal attack which in the beginning calls out radiation of pain to the left and later, with increasing intensity, also to the right, may be explained by a jumping over of the stimulus from the left to the right side in the spinal cord. Other investigators have suggested different possibilities, and each has supported his view with clinical observations.

Fundamental to Mainzer and Josephthal's investigations are the facts that the larger part of the left ventricle, especially in its entire anterior wall, is supplied with blood by the left coronary artery, whereas the right coronary artery supplies the greater part of the right ventricle and a portion of the posterior wall of the left ventricle. Therefore, if the seat of muscular injury is important in determining the radiation of anginal pain, it would be expected that circulatory disturbances involving the left coronary artery would be associated with radiation of pain to the left, while circulatory disturbances involving the right coronary artery would be associated with radiation of pain to the right.

A carefully selected group of patients with angina pectoris were studied and classified as having pain with a central localization or with right-sided or left-sided radiation or both, and the electrocardiograms were classified as revealing an injury in the anterior or in the posterior wall or of indefinite localization. To the authors' 39 cases were added reports of 38 more by authors who made similarly careful observations.

44. Mainzer, F., and Josephthal, F.: Ueber die Lokalisation und Ausstrahlung des Angina pectoris-Schmerzes, Acta med. Scandinav. **89**:329, 1936.

The accompanying table gives the combined figures. The results are obviously discordant and require explanation. The thought that the localizing possibilities of the electrocardiogram were overvalued is inadmissible. That this is not the case is shown by the general agreement with the observations of Buchner, Weber and Haager, whose studies were anatomically controlled. Mainzer and Josephthal said they feel that the true explanation lies in the consideration of the differences between coronary insufficiency of the right and of the left ventricles. In most patients with angina pectoris there is significant hypertrophy of the left ventricle due to previous or present arterial hypertension. Now the discrepancy between the maximal coronary flow to a normal muscle mass and a pathologically increased muscle mass is a decrease in flow to the latter; the maximal diameter of the coronary vessels is set once and for all. With the development of coronary arteriosclerosis, the relative functional insufficiency of the left ventricle becomes marked indeed. This is true to such a degree that even in predominant disease of the right coronary artery it is the overworked and hypertrophied left ventricle which comes to harm through the functional inter-

Left-Sided Pain					Central Pain				Right-Sided Pain				Right-Sided and Left-Sided Pain			
Total	Anterior Wall	Posterior Wall	Anterior and Posterior Wall (Indefinite)	Normal	Total	Anterior Wall	Posterior Wall	Anterior and Posterior Wall (Indefinite)	Total	Anterior Wall	Posterior Wall	Anterior and Posterior Wall (Indefinite)	Total	Anterior Wall	Posterior Wall	Anterior and Posterior Wall (Indefinite)
37	11	13	11	2	30	17	4	9	6	2	3	1	4	1	1	2

dependence of both circulatory territories. This explanation is in full agreement with the anatomic findings; not only in all cases of arteriosclerosis of the left coronary artery and of the narrowing of the mouths of both coronary arteries by syphilis but also in all cases of anatomic stenosis of the right coronary artery, the myocardial lesions lie in the region of the left ventricle. In those anginal attacks in which the progressive radiation of the pain depends on the strength of the attack, it is explained that with increasing intensity of the attacks the ischemic area extends to a location which will provoke the particular radiation observed.

There is little new to discuss concerning the treatment of angina pectoris.[45] Of the various operative procedures, injection of alcohol

45. Beck, C. S.: Further Data on Establishment of a New Blood Supply to the Heart by Operation, J. Thoracic Surg. **5**:604, 1936. Kerr, H. H.: Results of Superior Cervical Sympathectomy in Angina Pectoris, South. Surgeon **5**:365, 1936. Feinberg, S. C.: Treatment of Coronary Artery Disease by Intravenous Injections of Hypertonic Saline Solution, Am. J. M. Sc. **191**:410, 1936. Barach, A. L.; Richards, D. W., and Parsons, W. B.: Oxygen Treatment and Thyroid Ablation in Treatment of Heart Disease, Ann. Int. Med. **9**:1453, 1936.

into the communicating rami of the upper dorsal sympathetic nerves continues to be the most satisfactory.

Coronary Thrombosis.—Wiggers and Green [46] have experimentally investigated the effectiveness of drugs on collateral flow after experimental coronary occlusion in dogs. They have pointed out the many difficulties attending this problem. Observations of changes in color or comparison of size of infarcts without and with the use of a drug are subject to too many contingencies to have certain value. Testing the effects of drugs on coronary outflow or inflow does not test the response of collateral vessels, and it ignores the hemodynamic alterations resulting from occlusion of the main branch.

Attempts were made to establish a reliable criterion for determining changes in collateral coronary flow. Measuring blood flow from the distal end of a cut coronary artery was deemed too hazardous a method, both because the blood need not have passed through the infarcted area and because of the difficulty in registering the minute changes in flow. During the early phases of their work these authors saw no reason for questioning the view generally held that the pressure in the peripheral end of a cut coronary vessel represents the pressure transmitted through various collaterals and that it constitutes the pressure head for collateral coronary flow. However, it was shown in another study that this peripheral coronary pressure is due not to transmission of waves of arterial pressure but to the compressing action of the ventricle on intramural vessels and therefore does not serve as an index of collateral coronary flow.

The supposition was then considered that changes in the rate of coronary inflow of a perfused artery of the intact heart can be used as a criterion not only of changes in the flow through its distributing intramural branches but of changes in collateral supply as well. It was believed at first that changes in vascular resistance induced by drugs could probably be referred solely to vascular changes, because the ischemic region studied was not contracting. Other studies showed, however, that peripheral coronary resistance is increased just about as much when the area is stretched by the force of intraventricular tension as when tension develops through its own contraction. Thus, while this method is unsuitable as a criterion for determining alterations of collateral flow alone to an ischemic area following the use of drugs, it does offer a criterion of the changes in resistance to flow which are

46. Wiggers, C. J., and Green, H. D.: The Ineffectiveness of Drugs upon Collateral Flow After Experimental Coronary Occlusion in Dogs, Am. Heart J. **11**:527, 1936.

the result of vasomotor and extravascular effects which inescapably operate together. Since the conditions resemble those following coronary occlusion in man, this method is of considerable practical importance.

It was found that drugs of the theobromine and theophylline group and alcohol, which cause insignificant changes in mean arterial pressure, have a negligible effect on flow through an ischemic region. The nitrite group, which causes a fall in mean arterial pressure, produces a slight decrease in coronary resistance within the ischemic area. This is probably due to decrease in extra-arterial compression of coronary vessels following lowered arterial pressure, with decrease in the stretch of the ischemic area, rather than to dilatation of the vessels in this area. In any event, this slightly beneficial effect is more than offset by the lowering of pressure in other branches from which collateral flow could be derived. Pressor drugs, such as epinephrine, increase resistance to inflow in the ischemic area; if these drugs exert a dilating vascular action, it is overpowered by a greater extravascular pressure in the intact heart. The effect of 5 to 10 per cent carbon dioxide with oxygen was negligible, but in three experiments partial asphyxiation caused a slight decrease in minute flow each time.

The problem of collateral flow was attacked from yet another standpoint. It was shown previously, by means of myographs, that the muscular area supplied by the ramus descendens ceases to contract and vigorously expands within about one minute after occlusion of this artery. Now if a drug acts to increase significantly the collateral blood supply, its injection from one to two minutes after occlusion should cause some amelioration of the systolic muscular expansion and perhaps some sign of contractile recovery, such as promptly follows unclamping of the main artery. The results obtained show that the abolition of contraction after occlusion of the ramus descendens is not modified in the least by inhalation of oxygen, carbon dioxide or amyl nitrite or by therapeutic intravenous doses of various theophylline preparations, nitrites, adenylic acid or epinephrine.

The general conclusion is reached that under the experimental conditions described the collateral blood supply to an ischemic area cannot be significantly improved by the use of any drug. We feel that these experiments extend considerably the knowledge of rational treatment of acute cardiac infarction. Certainly clinical observations in most cases are in agreement. Whether these results are equally applicable to instances of sudden occlusion of small coronary arteries or to the gradual occlusion of larger ones requires further consideration. For example, the partial or complete relief of pain in some

instances of cardiac infarction following the use of vasodilating drugs has been held generally to indicate a favorable effect. This might be accomplished either by increasing the coronary flow in the infarcted area or by decreasing the work of the heart; but in either event the result would be beneficial.

Meanwhile, clinical experience continues to show the value of vasodilating drugs for occasional patients who suffer from paroxysmal angina pectoris. The mechanism by which this salutary effect occurs and the type of patient who is likely to respond favorably have not been made clear.

There have been a large number of clinical reports concerning various aspects of coronary thrombosis, of which only a few can be listed here.[47] An excellent monograph on diseases of the coronary arteries has been published under the editorship of Levy.[48]

MISCELLANEOUS CARDIAC DISORDERS

Amyloidosis.—There have recently been reported a number of cases of myocardial amyloidosis.[49] The heart may be affected as part of a widespread process, or it may be the chief organ involved. Only rarely is the cardiac involvement sufficient to produce congestive failure. The diagnosis is extremely difficult during life, especially in the idiopathic variety, which is not associated with preceding or concurrent chronic disease.

Nonbacterial Thrombotic Endocarditis.—Gross and Friedberg [50] have described in detail the clinical and pathologic features in 47 cases of nonbacterial thrombotic endocarditis. They have classified their cases

47. Edeiken, J., and Wolferth, C. C.: Persistent Pain in the Shoulder Region Following Myocardial Infarction, Am. J. M. Sc. **191**:201, 1936. Shookhoff, C.; Douglas, A. H., and Rabinowitz, M. A.: The Sedimentation Time in Acute Cardiac Infarction, Ann. Int. Med. **9**:1101, 1936. Goodrich, B. E., and Smith, F. J.: Nonfilament Leukocyte Count After Coronary Artery Occlusion, Am. Heart J. **11**:581, 1936. Blumer, G.: Pericarditis Epistenocardica, J. A. M. A. **107**:178 (July 18) 1936. Raab, A. P., and Rabinowitz, M. A.: Glycosuria and Hyperglycemia in Coronary Thrombosis, ibid. **106**:1705 (May 16) 1936.

48. Levy, R. L.: Diseases of the Coronary Arteries and Cardiac Pain, New York, The Macmillan Company, 1936.

49. Kerwin, A. J.: Idiopathic Amyloid Disease of the Heart, J. Lab. & Clin. Med. **22**:255, 1936. Ferris, H. W.: Amyloidosis of Lungs and Heart, Am. J. Path. **12**:701, 1936. Perla, D., and Gross, H.: Atypical Amyloid Disease, ibid. **11**:93, 1935. Reimann, H. A.; Koucky, R. F., and Eklund, C. M.: Primary Amyloidosis Limited to Tissue of Mesodermal Origin, ibid. **11**:977, 1935.

50. Gross, L., and Friedberg, C. K.: Nonbacterial Thrombotic Endocarditis: Classification and General Description, Arch. Int. Med. **58**:620 Oct.) 1936. Friedberg, C. K., and Gross, L.: Nonbacterial Thrombotic Endocarditis Associated with Acute Thrombocytopenic Purpura, ibid. **58**:641 (Oct.) 1936.

into five groups and have presented the distinguishing features of each. This disorder is viewed by them as an accidental occurrence in the course of any fatal disease and as without appreciable significance. Its development is usually dependent on previous rheumatic damage to the cardiac valves, but occasionally it may be dependent on some toxic agent which appears to have a special predilection for endothelial structures.

Pellagra.—Feil [51] has stated that acute pellagra is frequently associated with cardiovascular symptoms, including dyspnea, palpitation, tachycardia, feeble heart sounds and slight edema in some instances. The electrocardiogram was abnormal in 19 of the 38 cases studied, and in only 4 of the 19 was there any complication which might have been a factor in causing the electrocardiographic alterations. Although manifestations of cardiac disorder in pellagra are common, they are not as a rule severe.

Typhus Fever.—Herzog and Rodriguez [52] systematically investigated the pathologic changes in the heart in 103 cases of typhus fever during the last epidemic in Chile. Whereas macroscopically, save in a few instances, there were no detectable changes save dilatation of the left ventricle and flabbiness of the cardiac muscle, microscopically, 97 per cent of the patients showed specific, disseminated, mostly focal interstitial myocarditis. These lesions were carefully studied and described. A special investigation of the conduction system revealed little abnormality, and this was borne out by electrocardiographic studies. The authors did not include a clinical description of the patients, but they stated that the severity of the heart failure paralleled the pathologic picture.

Carbon Monoxide Poisoning.—Kroetz [53] has emphasized the cardiac signs and symptoms of carbon monoxide poisoning. These cardiac symptoms have been little noted, partly because of the prominence of other symptoms and partly because rescue workers are rarely trained observers.

Palpitation is the most remarkable circulatory symptom and is found without exception after this type of poisoning. According to Lewin, in the terrific explosion at Lengherydd, Wales, which resulted in the death of 440 miners, many of the rescue crew had such marked

51. Feil, H.: A Clinical Study of the Electrocardiogram and of the Phases of Cardiac Systole in Pellagra, Am. Heart J. **11**:173, 1936.

52. Herzog, E., and Rodriguez, H.: Die Beteiligung des Myocards beim Fleckfieber (Myocarditis exanthematica), Beitr. z. path. Anat. u. z. allg. Path. **96**:431, 1936.

53. Kroetz, C.: Herzschädigungen nach Kohlenoxydvergiftungen, Deutsche med. Wchnschr. **62**:1365, 1936.

palpitation that it was heard by their comrades and mistaken for the knocking of the entombed miners.

Disturbances of rhythm frequently, but not always, accompany the palpitation. The heart rates of previously healthy persons are found to be between 100 and 140 a minute, and this tachycardia is followed in a few days by bradycardia, often associated with high grade auriculoventricular block.

Pain of an anginal character, with typical radiation, may appear if the inhalation of gas does not lead to unconsciousness. This is often masked by other complaints, including cough, suffocation and pain in the region of the diaphragm and in the back. In some instances actual pain may be absent, but there may be a feeling of injury in the heart. Kroetz has pointed out that anginal pain may be present without the typical picture of carbon monoxide poisoning, which may be lacking because of the accompanying severe circulatory shock. There may be toxic myocarditis, which is declared by cardiac dilatation, by lowering of the blood pressure and by alteration in the heart sounds, rate and rhythm.

The electrocardiographic alterations, which were long thought to be exceptional, are regular, reliable and differentially valuable signs. These alterations are more significant and usually outlast the clinical cardiac symptoms. They include abnormalities of the P wave, prolongation of the auriculoventricular conduction time, intraventricular block and alterations in the ST segment and T wave suggesting coronary disease.

The Athletic Heart.—Kirch [54] has added to his previous detailed studies concerning the possibility of real hypertrophy of the heart consequent to prolonged athletic training. He has said that he feels that this problem cannot be satisfactorily determined by clinical investigation only but that it must be correlated with painstaking anatomic observations. The material chiefly consisted of the hearts of 9 athletes who died suddenly between the ages of 15 and 25. They had all been healthy previously and without cardiac complaints. Painstaking anatomic studies were made, including weighing the cardiac chambers separately, measuring these chambers in various ways and relating the findings to body weight and to skeletal musculature.

It is impossible here to do more than summarize briefly Kirch's conclusions. Three of the nine hearts showed definite hypertrophy. The author would reserve the term athlete's heart for such an anomaly only. The athletic heart is not a diseased heart; the hypertrophy must be considered solely as a process of adjustment, which will be reversed

54. Kirch, E.: Herzkräftigung und echte Herzhypertrophie durch Sport, Ztschr. f. Kreislaufforsch. **28**:893, 1936.

as soon as the athletic activity is decreased or stopped. Whether this hypertrophy follows dilatation, as is so often true in the usual instances of cardiac hypertrophy, the author was unable to decide; he was never able to associate cardiac weakness and myocardial dilatation with the athletic heart. Often the term athletic heart is applied improperly in instances of cardiac dilatation, which is more truly an expression of cardiac weakness. Three of the nine hearts were normal, and the remaining three were slightly enlarged, occupying an intermediate place between normal size and frank hypertrophy. The author used the term *gekraftigten Herzen* (strengthened hearts) to separate them from unmistakably hypertrophied (athletic) hearts.

Neurocirculatory Asthenia.—Johnson [55] became interested in a group of patients many of whom had complaints suggesting neurocirculatory asthenia and found the chloride level of the blood abnormally low. These patients were symptomatically relieved within four or five days by increasing the intake of sodium chloride. It may well be that a small percentage of patients now wrongly classified as neurasthenic may in reality be suffering from the effects of abnormally low chloride values.

CARDIAC ARRHYTHMIAS

Orgain, Wolff and White [56] have reviewed the pertinent literature and reported their studies of a series of 54 patients with auricular fibrillation and auricular flutter and without other signs of cardiac disease. Forty-seven of the 54 patients had auricular fibrillation alone, 5 had auricular flutter alone and 2 had both. The ages of the 49 patients with auricular fibrillation ranged from 21 to 75 years. The arrhythmia was paroxysmal in all but 3 cases. Definite etiologic factors were few, but many of the attacks were intimately associated with such precipitating factors as infection, alcohol, ether, burns, colic in the gallbladder, vomiting, surgical operation, exertion and emotion. Follow-up studies of 90 per cent of the entire group revealed that the prognosis for life and for the maintenance of adequate cardiac function is good. Reassurance, the avoidance of precipitating factors and the use of quinidine sulfate were regarded as the most useful therapeutic measures.

The ages of the 7 patients with auricular flutter varied from 27 to 66 years. All the attacks were paroxysmal, the duration varying from a few minutes to five years. The common symptoms were palpitation,

55. Johnson, A. S.: Sodium Chloride Therapy, New England J. Med. **215**:438, 1936.

56. Orgain, E. S.; Wolff, L., and White, P. D.: Uncomplicated Auricular Fibrillation and Auricular Flutter: Frequent Occurrence and Good Prognosis in Patients Without Other Evidence of Cardiac Disease, Arch. Int. Med. **57**:493 (March) 1936.

choking, dyspnea, dizziness, weakness and, occasionally, precordial pain. The precipitating factors were exertion, surgical operation and infection. Quinidine or quinine was used in 5 cases, being effective in restoring normal rhythm or preventing paroxysms in 3, but later proving ineffective in 1 of these. Digitalis restored normal rhythm in 1 of 5 cases in which it was tried. Quinidine, after treatment with digitalis, converted the rhythm to normal in 2 instances.

Campbell and Gordon [57] have reported on the use of quinidine in a series of 135 cases of auricular fibrillation. This drug restored normal rhythm in about two-thirds (64 per cent) and was effective in maintaining normal rhythm in about one-third (34 per cent).

It is emphasized that restoring normal rhythm and, even more so, maintaining it for a long period depend on the careful selection of suitable patients. In general, the most suitable patients are those without congestive failure or marked valvular disease, with no more than slight cardiac enlargement, in whom fibrillation has been established for less than one month.

Thorough treatment with digitalis is important before treatment with quinidine is started. Any complicating infection may prevent success. In 7 of the 135 cases embolism developed after treatment, and in only 1 instance was there a fatality which was probably due to quinidine.

Starr [58] reported on the use of acetylbetamethylcholine in the treatment of seventy-five attacks of paroxysmal tachycardia in 37 patients. He outlined the method as follows: The patient is asked to lie down. Alternate pressure over the carotid sinuses is attempted; and if this is unsuccessful in stopping the arrhythmia, acetylbetamethylcholine is given subcutaneously. If the attack does not stop promptly after the appearance of the flush, the site of the injection is vigorously massaged. If tachycardia persists, the carotid sinuses are alternately compressed while the action of the drug is undiminished. If this is unsuccessful, larger doses of the drug may be given.

Dosage varies with weight and age. For children, 10 mg. may be sufficient to stop an attack, while for elderly obese persons as much as 60 mg. may be necessary; an average dose is 30 mg. It is important to massage the site of the injection if a given dose is ineffective or even to increase the dose. By mistake as much as 30 mg. has been given intravenously and 300 mg. subcutaneously without fatal results. In instances of toxicity, atropine should be given. An antagonism exists

57. Campbell, M., and Gordon, F. W.: The Quinidine Treatment of Auricular Fibrillation, Quart. J. Med. **5**:205, 1936.

58. Starr, I.: Acetyl-β-methylcholin: IV. Further Studies of Its Action in Paroxysmal Tachycardia and in Certain Other Disturbances of Cardiac Rhythm, Am. J. M. Sc. **191**:210, 1936.

between the cardiac effects of acetylbetamethylcholine and quinidine, and these drugs should not be given together; the same is true, but in a lesser degree, in regard to digitalis.

Acetylbetamethylcholine is not very effective in the treatment of auricular flutter or ventricular extrasystoles, and no permanent effect follows its use in auricular fibrillation.

Gravier and his co-workers [59] were able to cure a patient with troublesome sino-auricular tachycardia by excision of the right stellate ganglion.

An abstract of the case report follows:

> This patient was a woman aged 37 years whose heart rate was habitually moderate and was not increased unduly by effort, food or emotion. In the course of the menstrual period, however, the heart rate increased to 140 to 180 per minute and was accompanied with distressing symptoms, preventing her from leading a normal existence. Not only was medicinal therapy ineffective, but it seemed to increase the tachycardia, and as a last resort the right stellate ganglion was removed. This procedure effected a complete cure.

The authors have discussed the nature of the abnormal cardiac mechanism in this case and the rationale of treatment.

HEART FAILURE AND ITS TREATMENT

Peters and Visscher [60] have investigated the energetics of the heart in the heart-lung preparation under various conditions. They emphasize

> that the most important characteristic of any machine during work is its efficiency. The heart is a machine for transforming chemical potential energy into work in transporting blood around the circulatory system. The amount of energy it must expend in order to perform a given amount of work is of profound importance in the physiology, and especially in the pathological physiology, of the heart.

Their results indicated that the failing heart suffers first simply from a decrease in mechanical efficiency. The energy liberated at a given external diastolic volume remains the same; only the proportion which can be put to useful work falls off. Heart failure consists, in essence, of an alteration of the energy-utilizing and not the energy-liberating mechanism; the heart is able to liberate energy, but it is unable to put it to useful work. The authors stated the belief that the correction of this defect should be the physiologic objective in the treatment of myocardial failure.

Various substances were tested in regard to their ability to alter the capacity of the heart for work. It was shown that at constant external diastolic volume, both calcium and glucosides of the digitalis

59. Gravier, L.; Tourniaire, A., and Gonnet, J.: Nevrose tachycardique traitée par stellectomie droite, Lyon méd. **158**:425, 1936.

60. Peters, H. C., and Visscher, M. B.: The Energy Metabolism of the Heart in Failure and the Influence of Drugs upon It, Am. Heart J. **11**:273, 1936.

series increase the consumption of oxygen and the efficiency of the cardiac muscle. Several reputed cardiac tonics have no direct beneficial action on the heart; for example, coramine (pyridine betacorbonic acid diethylamine in a 25 per cent solution) produces, instead, dilatation with decreased output and efficiency.

Thompson and White [61] have concluded from a review of 2,000 postmortem examinations that the commonest cause of hypertrophy of the right ventricle is strain and failure of the left ventricle. In 704 of the 2,000 cases there was hypertrophy of the right ventricle to the extent that the wall measured 5 mm. or more in thickness. Of these 704 cases, clinical study revealed factors producing primary strain of the right ventricle in 64, primary strain of the left ventricle in 326, primary strain of both ventricles in 141 and no clear cause of strain in 141. Thus, in nearly half the cases the only cause of hypertrophy of the right ventricle was strain and hypertrophy of the left ventricle. Right-sided hypertrophy was often found in cases of pure left-sided strain, regardless of the presence or absence of clear clinical evidence of failure of the left ventricle, but the presence of failure increased the degree of hypertrophy. It was found that the degree of hypertrophy of the right ventricle was almost as great in cases of pure left-sided strain as it was when there had been primary right-sided strain.

Parker and Weiss [62] have described the changes in the blood vessels and alveolar walls in the lungs in cases in which there was an advanced degree of rigid mitral stenosis associated with extreme failure of the pulmonary circulation. Their description of these changes follows:

> The lesions in the pulmonary vessels consisted of (*a*) intimal thickening of the arteries, and (*b*) hyperplastic arteriolar sclerosis and arteriolar necrosis. The changes in the alveolar wall consisted of (*a*) marked dilatation of the capillaries, (*b*) increase in the thickness of the capillary basement membrane, (*c*) increase in the interstitial tissue (collagen), (*d*) interstitial pericapillary edema, and (*e*) a tendency of the flat epithelial cells to become cuboidal in shape. . . .
>
> With progressive pulmonary engorgement, first the visible capillaries increase in number, and only later do they dilate. Often the capillaries become displaced and are separated from the alveolar surface by a considerable degree of edema or by thick layers of collagen.
>
> Permanent structural alterations in the lungs caused by circulatory failure interfere with the gaseous exchange, partly through altered permeability of the alveolar wall, and partly as a result of the simultaneous passage through the individual capillaries of numerous columns of red cells, instead of a single red cell.

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61. Thompson, W. P., and White, P. D.: The Commonest Cause of Hypertrophy of the Right Ventricle—Left Ventricular Strain and Failure, Am. Heart J. **12**:641, 1936.

62. Parker, F., Jr., and Weiss, S.: The Nature and Significance of the Structural Changes in the Lungs in Mitral Stenosis, Am. J. Path. **12**:573, 1936.

In the causation of the pulmonary arterial and arteriolar lesions, an important rôle is played by the prolonged combined presence of (*a*) high intravascular pressure, (*b*) stagnation of blood, and (*c*) edema.

Coelho and Ribeiro [63] observed acute pulmonary edema in man, which, in the order of frequency, is caused by failure of the left ventricle, mitral stenosis, toxic states and cerebral disturbances. They said they recognize that there are additional causes which have been noted by other authors. They found that the mechanism of pulmonary edema produced in dogs by the injection of silver nitrate in the right ventricle or saphenous vein is different from the edema produced by injury to the left ventricle or complete obstruction of the aorta. In the former instances the edema is of toxic origin and identical with toxic edema in man; in the latter instances the edema is of mechanical origin and is identical with pulmonary edema produced in man by insufficiency of the left ventricle.

Smirk [64] has ably discussed certain factors which favor the development of edema in congestive heart failure.

Many observers have shown that the albumin and globulin percentages of the plasma are substantially lower in most cases of congestive heart failure, and, in general, the lesser the percentages the greater the edema. Furthermore, it has been shown that improvement in congestive failure is accompanied with a return of the colloid osmotic pressure toward normal. Smirk's observations showed that the average degree of difference in the colloid osmotic pressure of the plasma for groups of normal patients and of patients with heart failure is in the region of 6 to 10 cm. of water.

The colloid osmotic pressure of samples of edema fluid removed from patients with congestive heart failure is ordinarily between 2 and 6 cm. of water. Thus the low colloid osmotic pressure of the plasma and the presence of a colloid osmotic pressure in the edema fluid both reduce the effective osmotic pressure of the plasma. The reduction may be only a few centimeters or as great as 18 cm. of water. It is a well known fact that, apart from congestive heart failure, one may have a fall in the osmotic pressure of the plasma of 10 or 15 cm. of water below the normal without the development of edema, and one may deduce that the fall in the effective osmotic pressure in congestive heart failure is usually insufficient of itself to insure the development of edema.

63. Coelho, E., and Ribeiro, M.: Etude expérimentale sur deux formes pathogéniques de l'oedème du poumon: mécanique et toxique, Arch. d. mal. du cœur **29**:383, 1936.

64. Smirk, F. H.: Observations on the Causes of Oedema in Congestive Heart Failure, Clin. Sc. **2**:317, 1936.

Smirk next considered whether the capillaries in congestive heart failure and in health are equally permeable to water with its dissolved crystalloids. This was studied by comparing the rates of passage of fluid out from blood vessels under equal filtration pressures. The results indicated that if the average transudation rate is called 100 per cent in the normal, it is 200 per cent in the experiments in which a correction is applied for the low colloid osmotic pressure of the plasma and 260 per cent in the experiments in which no such correction is made.

The relationship between venous pressure and edema also was studied. Smirk mentioned some of the variables to be considered in relating an increase in the venous pressure to the formation of edema. Although a straight line relationship has been shown between the degree of artificial venous congestion in normal human subjects at rest and the rate of formation of edema, it is felt that this should be regarded as a remarkable coincidence rather than strong evidence that edema fluid is a simple filtrate of plasma and that a balance of the forces of the capillary pressure and of the osmotic pressure of the plasma is largely responsible for the interchange of fluid through the capillary blood vessels.

In resting patients with congestive heart failure the venous pressure in the legs is a few centimeters less than the general venous pressure plus the pressure of a vertical column of water extending from the manubrium to the place where the venous pressure is measured; the same is true for normal subjects. Active muscular movements of the legs diminish this pressure by from 10 to 100 cm. of water. Thus the incapacity for exercise of patients with congestive heart failure increases the average venous pressure in the legs throughout the day to much above normal. In congestive heart failure the general venous pressure, measured in relation to the manubrium, seldom exceeds 10 cm. of water. At rest a rise of 10 cm. in general venous pressure will produce a rise of about 10 cm. in the veins of the leg, but the average rise of pressure throughout the capillary bed is less than the rise of venous pressure which causes it. Many good arguments are given to show that a uniform rise of 10 cm. of water in capillary pressure, apart from its secondary effects on blood vessels, is insufficient in itself to cause edema. However, such an increase in filtration pressure will naturally increase the transudation of fluid from blood vessels.

It is clear that in many cases of congestive heart failure several factors acting in varying degree contribute toward the development of edema; their importance in regard to treatment is obvious.

Kalter [65] has used amino-acetic acid in degenerative heart disease and congestive heart failure. The theoretical basis for the use of amino-acetic acid in cardiac disease is made clear, and an analogy is drawn with its use in progressive muscular dystrophy. Cases are cited in which amino-acetic acid was apparently of considerable benefit in the treatment of cardiac failure. We have used this drug in a few cases of heart failure, with definite benefit in 2 instances.

65. Kalter, S.: Ueber Glykokollbehandlung degenerativdystrophischer Herzmuskelerkrankungen, Deutsche med. Wchnschr. **62**:1371, 1936.

Book Reviews

Parenteral Therapy: A Ready Reference Manual of Extra-Oral Medication. By Walton Forest Dutton, M.D., and George Burt Lake, M.D. Cloth. Price, $7.50. Pp. 386, with 90 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1936.

It is the usual task of the reviewer to set before his readers the reasons for buying or reading any new work that is brought to his attention. If there are no such reasons, the work is, as a general rule, ignored. Occasionally, it becomes the reviewer's unpleasant duty to point out the general worthlessness of a book and even its potential dangers.

The book under present consideration is divided into three sections. The first deals with the general technic of parenteral therapy. It includes descriptions of the methods of giving or attempting to give medicaments by all the parenteral routes now in use. It discusses blood transfusion, intracardiac injections, pneumothorax and paracentesis of all the serous spaces. It describes surgical procedure such as the administration of an anesthetic, the treatment of injection of material into the veins and the injection treatment of hernia.

This part of the work is well done. The authors make no claim to originality. They have merely collected data on the well known methods. One wonders why it should have been done at all. Surely, a textbook is not needed to describe the technic of hypodermic and simple intravenous medication. These methods need no encouragement; they are overdone now. The more complicated methods are in the nature of major surgical procedures and should not be attempted by any one without an adequate period of training. Thyroidectomy or cholecystectomy should not be attempted with no further training than a perusal of a description of the technic. Neither should cisternal puncture or ventricular puncture or even blood transfusion be performed. There is even less excuse for the publication of the second and third parts of the book. The second part is a therapeutic index. Here are listed diseases and under each the drugs (parenteral) that may be used to advantage. One learns that alopecia may be treated with salts of arsenic, antuitrin, pilocarpine or glycerophosphates. Asexualism yields to testicular, ovarian and pluriglandular preparations or viriligen. A journey to the lower end of the alphabetic list informs one that goiter vaccine (Houda) is recommended in both thyroid deficiency and thyrotoxicosis. And so on, ad nauseam.

The third portion consists of pharmacologic notes. This is an alphabetic arrangement of a large number of drugs all of which lend themselves to parenteral administration. Most of these drugs are listed under their trade names, and the manufacturer is not neglected. It is impossible to mention all the ridiculous compounds that have found their way into this collection. Adrempco is a solution representing the entire pituitary, thyroid and adrenal glands and the ovaries and testicles. The list of gold preparations reminds one of Thompson's work entitled "The Quacks of Old London." Again one meets goiter vaccine (Houda) and viriligen, and one finds the remarkable statement that strychnine is marketed by Merck & Co., Inc., and others.

The authors state in the preface that they have not had personal experience with all the drugs listed in the index and naively remark that they have studied the statements of the manufacturers but assume no responsibility for the results that may follow the use of any of these remedies. This does not constitute a valid excuse. Since the publication and discussion of a remedy implies tacit approval unless the reverse is stated, it seems that these authors have assumed a weighty responsibility.

Considerable time has been spent by the reviewer in saying what might have been said in a few words; namely, this book should never have been released.

Die Nebennierenrinde. By Sigismund Thaddea, M.D. Price, 11 marks. Pp. 199, with 78 illustrations and 36 tables. Leipzig: Georg Thieme, 1936.

The author of this monograph is an assistant in the Second Medical University Clinic of the Charité Hospital in Berlin. He has painstakingly assembled the material for a review of the development of knowledge concerning the adrenal cortex from the original description of the adrenal glands by Eustachius in 1563 down to the present time. He is to be congratulated on the success of his work. The author has arranged his material according to a well planned sequence. He begins with a historic account of the adrenal glands, next he discusses the morphology and function of the adrenal cortex and then he describes the isolation of the cortical hormone and animal experiments to prove the many effects of this hormone. Finally, he devotes a section of the book to the clinical aspects of Addison's disease and other conditions in which the function of the adrenal cortex is deficient and to the treatment of these conditions that may be logically employed. A bibliography of 640 well chosen references, arranged in alphabetic order and covering the literature of the entire world, is included.

A monograph of this character, well put together and well printed and accompanied with clear illustrations, cannot fail to be serviceable. It will be of use largely for reference purposes to medical students and teachers and therefore should soon be available in any good library to which students have access.

Le diabète sucré: Questions controversées de clinique et de pathogénie. By E. Aubertin, E. Bessière, P. Broustet, O. Hirsch, P. Mauriac, R. Saric, M. Traissac and F. J. Traissac. Price, 32 francs. Pp. 214. Paris: Masson & Cie, 1936.

This book consists of a series of lectures by various physicians at the hospital Saint-André de Bordeaux on different aspects of diabetes, such as nervous complications, ocular complications and intermittent diabetes. The material is of some interest but is not new for the most part.

La syphilis gastrique. By Anastase Landau and Joseph Held. Price, 32 francs. Pp. 185. Paris: Masson & Cie, 1936.

Landau and Held thoroughly present the subject of gastric syphilis in this monograph. They include not only organic gastric disease but functional gastric disturbances due to extragastric syphilis. The monograph includes a discussion of the incidence, pathology, classification and treatment of the disease, the disturbances in the secretory function of the stomach as a result of syphilis and the difficulties encountered in making a differential diagnosis of gastric syphilis. It includes also a good bibliography, mostly of French and German works and many x-ray plates.

Nothing particularly new is added to the subject; however, the monograph is a good clinical discussion of gastric syphilis.

Theory and Practice of Psychiatry. By William Sadler. Price, $10. Pp. 1231. St. Louis: C. V. Mosby Company, 1936.

Dr. Sadler gives an excellent and comprehensive discussion of his subject without going to extremes. He rides no special hobby, shows no signs of psychiatric "cultism" and evolves no new philosophy. On running through this excellent compendium, the reviewer (who is not a professional psychiatrist) is impressed anew, however, with the difficulties of the whole subject. The psychiatrist of the modern school tends to state in technical and often incomprehensible terms what is fairly obvious to any one dealing with patients; one is consumed by the heat but obtains little light. A feeling becomes uppermost that perhaps methods of case finding and classification have outrun useful therapy. After all, the constitutional basis must be paramount in most of the unhappy persons who drift into the psychiatrist's net, and, while the writer does not mimimize this fact, he dismisses it in a relatively brief section.